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**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES**

Applicant: H. William Bosch
Title: NOVEL TRIAMCINOLONE COMPOSITIONS
Appl. No.: 10/697,716
Filing Date: 10/31/2003
Examiner: JEAN-LOUIS, Samira JM
Art Unit: 1617
Confirmation Number: 8372

BRIEF ON APPEAL

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REAL PARTY IN INTEREST

The real party in interest in this appeal is Elan Pharma International Ltd, which is the assignee of the present application as recorded at Reel/Frame numbers 015179/0523.

RELATED APPEALS AND INTERFERENCES

No related appeals or interferences are pending.

STATUS OF CLAIMS

Claims 1-3, 5-41, 43-108 are pending with claims 8, 15-16, 23-27, and 48-108 withdrawn from examination. Claims 1-3, 5-7, 9-14, 17-22, 28-41, and 43-47 are finally rejected, and are the subject of this appeal. The pending claims are presented in Appendix A of this Brief.

STATUS OF AMENDMENTS

As indicated in the final Office Action issued on September 15, 2009, claim amendments made in the Response to the non-final Office Action, filed on July 14, 2009, were entered. No other amendments are pending in the application.

SUMMARY OF CLAIMED SUBJECT MATTER

Independent claim 1 is to be argued in the brief. The relevant citation to the specification is shown in the parentheses below.

Independent claim 1 reads as follows:

1. A composition {p. 1, l. 24; p. 16, l. 21} comprising:
 - (a) particles of at least one triamcinolone or a salt thereof {p. 1, ll. 25-26; p. 16, ll. 22-23; p. 18, ll. 8-10}, wherein the triamcinolone particles have an effective average particle size of less than about 2000 nm {p. 1, l. 26 – p. 2, l. 1; p. 16, 26-28; p. 18, ll. 12-13} and have a phase selected from the group consisting of crystalline, amorphous, and semi-crystalline {p. 45, ll. 9-11}; and
 - (b) at least one surface stabilizer adsorbed on the surface of the triamcinolone particles {p. 2, ll. 1-3; p. 16, ll. 24-26; p. 18, ll. 10-11}, wherein said surface stabilizer is a surfactant {p. 46, ll. 11-12}.

GROUND OF REJECTION TO BE REVIEWED ON APPEAL

The rejections to be reviewed on appeal are the following:

1. Provisional rejection of claims 1-3, 5-6 and 14 on the ground of nonstatutory obviousness-type double patenting over claims 51, 60-61 and 64 of copending Application No. 12/320,431.
2. Provisional rejection of claims 1-3, 5, 11-12 and 14 on the ground of nonstatutory obviousness-type double patenting over claims 1-5, 8-10, 15 and 17 of copending Application No. 12/292,092.
3. Provisional rejection of claims 1, 5-7, 10-14, 33-36 and 39-40 on the ground of nonstatutory obviousness-type double patenting over claims 51, 60-61 and 64 of copending Application No. 12/117,982 in view of U.S. Patent No. 5,145,684 to Liversidge et al (“Liversidge”).
4. Provisional rejection of claims 1-3, 5-7, 9, 13-14 and 17 on the ground of nonstatutory obviousness-type double patenting over claims 1-17 of copending Application No. 12/052,436.
5. Provisional rejection of claims 1, 5 and 12-14 on the ground of nonstatutory obviousness-type double patenting over claims 10-12 and 19 of copending Application No. 12/051,448.
6. Provisional rejection of claims 1, 5-7, 9-11, 13-14, 21-22, 28-41 and 43 on the ground of nonstatutory obviousness-type double patenting over claims 1, 4-19 and 21-23 of copending Application No. 11/980,719 in view of Liversidge.

7. Provisional rejection of claims 1, 5-6, 9, 11-14 and 44-47 on the ground of nonstatutory obviousness-type double patenting over claims 1-4, 6, 8, 13-14 and 16-20 of copending Application No. 11/979,253.

8. Provisional rejection of claims 1, 5-7, 9, 11-14, 20, 28-31, 33-41 and 43 on the ground of nonstatutory obviousness-type double patenting over claims 1-3 and 5-19 of copending Application No. 11/761,900 in view of Liversidge.

9. Provisional rejection of claims 1, 5-7, 9-11, 13-14, 20-22, 28-32, 33-40 and 43 on the ground of nonstatutory obviousness-type double patenting over claims 1, 4-14, 17-19 and 21-23 of copending Application No. 11/436,887 in view of Liversidge.

10. Provisional rejection of claims 1-2, 5-7, 9-10 and 13-14 on the ground of nonstatutory obviousness-type double patenting over claims 1, 3-5, 9 and 18-21 of copending Application No. 11/376,553 in view of Liversidge.

11. Provisional rejection of claims 1, 5-7, 9-14, 18-21, 28-29 and 39-40 on the ground of nonstatutory obviousness-type double patenting over claims 1, 4-6, 8-9, 11-13, 15-16, 18-20, 24 and 27 of copending Application No. 11/275,069 in view of Liversidge.

12. Provisional rejection of claims 1, 5-7, 9-12, 14, 18-22, 28-29, 31, 33-41 and 43 on the ground of nonstatutory obviousness-type double patenting over claims 1-7, 9-12, 15-17 and 20-31 of copending Application No. 10/912,552 in view of Liversidge.

13. Provisional rejection of claims 1, 5-7, 9-14, 18-22, 28-29 and 33-38 on the ground of nonstatutory obviousness-type double patenting over claims 1-10, 12-24, 30, 34-35 and 38-39 of copending Application No. 10/895,405 in view of Liversidge.

14. Provisional rejection of claims 1, 5-7, 9-14, 17-22, 28-41 and 43-47 on the ground of nonstatutory obviousness-type double patenting over claims 1-38 of copending Application No. 10/768,194.

15. Provisional rejection of claims 1, 5-7, 9-14, 17-22, 28-41 and 43-47 on the ground of nonstatutory obviousness-type double patenting over claims 1-25 and 36-39 of copending Application No. 10/701,064 in view of Liversidge.

16. Provisional rejection of claims 1, 5-7, 9-14, 17-22, 28-41 and 43-47 on the ground of nonstatutory obviousness-type double patenting over claims 1-31, 36-38 and 40 of copending Application No. 10/697,703.

17. Provisional rejection of claims 1, 5, 9 and 13-14 on the ground of nonstatutory obviousness-type double patenting over claims 1-6 of copending Application No. 10/317,948.

18. Provisional rejection of claims 1, 5-7, 9-14, 18-22, 28-29 and 33-40 on the ground of nonstatutory obviousness-type double patenting over claims 1, 4-19 and 21-32 of copending Application No. 11/928,250 in view of Liversidge.

19. Provisional rejection of claims 1, 5-7, 9-14, 28-29, 33-41 and 43 on the ground of nonstatutory obviousness-type double patenting over claims 1, 4-19 and 21-32 of copending Application No. 11/367,716 in view of Liversidge.

20. Provisional rejection of claims 1, 5-7, 9-14, 17-22 and 33-36 on the ground of nonstatutory obviousness-type double patenting over claims 1-6 of copending Application No. 10/784,900.

21. Rejection of claims 1-3, 5-7, 9-14, 17-22, 28-41 and 43-47 under 35 U.S.C. §103(a) for allegedly being obvious over Liversidge in view of U.S. Patent No. 5,916,596 to Desai et al. ("Desai").

ARGUMENT

I. Rejection 1

The present application was filed on October 31, 2003, whereas Application No. 12/320,431 was later filed on January 26, 2009. Pursuant to MPEP 804, filing of a terminal disclaimer is not required in an earlier filed application to overcome a provisional nonstatutory obviousness-type double patenting rejection. The relevant passages of the MPEP is excerpted below:

If a "provisional" nonstatutory obviousness-type double patenting (ODP) rejection is the only rejection remaining in the earlier filed of the two pending applications, while the later-filed application is rejectable on other grounds, the examiner should withdraw that rejection and permit the earlier-filed application to issue as a patent without a terminal disclaimer. . . .

If "provisional" ODP rejections in two applications are the only rejections remaining in those applications, the examiner should withdraw the ODP rejection in the earlier filed application thereby permitting that application to issue without need of a terminal disclaimer. . . .

II. Rejection 2

The present application was filed on October 31, 2003, whereas Application No. 12/292,092 was later filed on November 12, 2008. As discussed *supra*, filing of a terminal disclaimer is not required in an earlier filed application to overcome a provisional nonstatutory obviousness-type double patenting rejection.

III. Rejection 3

The present application was filed on October 31, 2003, whereas Application No. 12/117,982 was later filed on May 9, 2008. As discussed *supra*, filing of a terminal disclaimer is not required in an earlier filed application to overcome a provisional nonstatutory obviousness-type double patenting rejection.

IV. Rejection 4

The present application was filed on October 31, 2003, whereas Application No. 12/052,436 was later filed on March 20, 2008. As discussed *supra*, filing of a terminal disclaimer is not required in an earlier filed application to overcome a provisional nonstatutory obviousness-type double patenting rejection.

V. Rejection 5

The present application was filed on October 31, 2003, whereas Application No. 12/051,448 was later filed on March 19, 2008. As discussed *supra*, filing of a terminal disclaimer is not required in an earlier filed application to overcome a provisional nonstatutory obviousness-type double patenting rejection.

VI. Rejection 6

The present application was filed on October 31, 2003, whereas Application No. 11/980,719 was later filed on October 31, 2007. As discussed *supra*, filing of a terminal disclaimer is not required in an earlier filed application to overcome a provisional nonstatutory obviousness-type double patenting rejection.

VII. Rejection 7

The present application was filed on October 31, 2003, whereas Application No. 11/979,253 was later filed on October 31, 2007. As discussed *supra*, filing of a terminal disclaimer is not required in an earlier filed application to overcome a provisional nonstatutory obviousness-type double patenting rejection.

VIII. Rejection 8

The present application was filed on October 31, 2003, whereas Application No. 11/761,900 was later filed on June 12, 2007. As discussed *supra*, filing of a terminal disclaimer

is not required in an earlier filed application to overcome a provisional nonstatutory obviousness-type double patenting rejection.

IX. Rejection 9

The present application was filed on October 31, 2003, whereas Application No. 11/436,887 was later filed on May 19, 2006. As discussed *supra*, filing of a terminal disclaimer is not required in an earlier filed application to overcome a provisional nonstatutory obviousness-type double patenting rejection.

X. Rejection 10

The present application was filed on October 31, 2003, whereas Application No. 11/376,553 was later filed on March 16, 2006. As discussed *supra*, filing of a terminal disclaimer is not required in an earlier filed application to overcome a provisional nonstatutory obviousness-type double patenting rejection.

XI. Rejection 11

The present application was filed on October 31, 2003, whereas Application No. 11/275,069 was later filed on December 7, 2005. As discussed *supra*, filing of a terminal disclaimer is not required in an earlier filed application to overcome a provisional nonstatutory obviousness-type double patenting rejection.

XII. Rejection 12

The present application was filed on October 31, 2003, whereas Application No. 10/912,552 was later filed on August 6, 2004. As discussed *supra*, filing of a terminal disclaimer is not required in an earlier filed application to overcome a provisional nonstatutory obviousness-type double patenting rejection.

XIII. Rejection 13

The present application was filed on October 31, 2003, whereas Application No. 10/895,405 was later filed on July 21, 2004. As discussed *supra*, filing of a terminal disclaimer is not required in an earlier filed application to overcome a provisional nonstatutory obviousness-type double patenting rejection.

XIV. Rejection 14

The present application was filed on October 31, 2003, whereas Application No. 10/768,194 was later filed on February 2, 2004. As discussed *supra*, filing of a terminal disclaimer is not required in an earlier filed application to overcome a provisional nonstatutory obviousness-type double patenting rejection.

XV. Rejection 15

The present application was filed on October 31, 2003, whereas Application No. 10/701,064 was later filed on November 5, 2003. As discussed *supra*, filing of a terminal disclaimer is not required in an earlier filed application to overcome a provisional nonstatutory obviousness-type double patenting rejection.

XVI. Rejection 16

The Examiner asserts that the pending claims are obvious over claims of copending Application No. 10/697,703 (“the ‘703 application”) directed to nanoparticulate nimesulide compositions.

The compositions of the ‘703 application are directed to nimesulide, which is a non-steroidal anti-inflammatory drug (NSAID), in contrast to the claimed triamcinolone compositions. The Examiner has failed to articulate that one skilled in the art would have considered it obvious to make a simple substitution of the active agent to achieve predictable results of obtaining the claimed nanoparticulate triamcinolone composition.

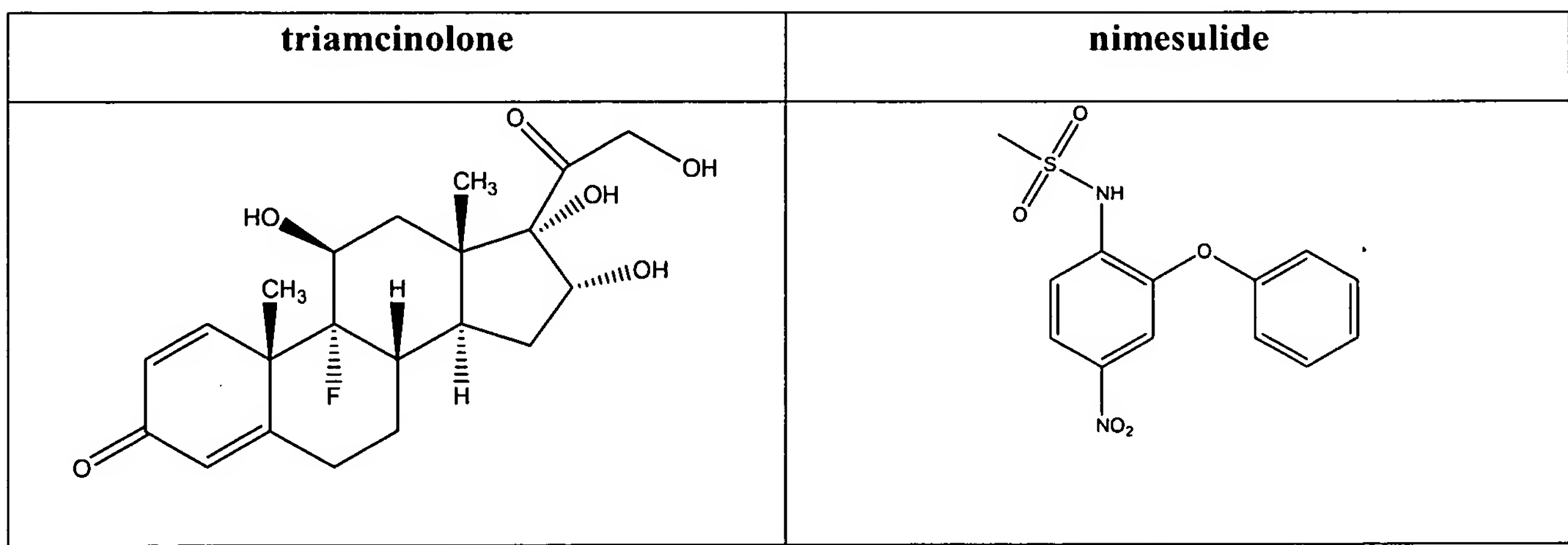
First, the U.S. Supreme Court's decision, *KSR International Co. v. Teleflex Inc.*, prompted a reconsideration of the simple substitution rationale, *i.e.*, positing the obviousness by simple substitution of one known element for another to obtain predictable results. *See* the EXAMINATION GUIDELINES FOR DETERMINING OBVIOUSNESS UNDER 35 U.S.C. §103..., published in the *Federal Register*, Vol. 72, No. 195 (October 10, 2007), hereafter "the Guidelines." Pursuant to the Guidelines, an examiner seeking to advance a simple substitution rationale is obliged to articulate:

- (1) a finding that the prior art contained a device (method, product, etc.) which differed from the claimed device by the substitution of some components (step, element, etc.) with other components;
- (2) A finding that the substituted components and their functions were known in the art;
- (3) a finding that one of ordinary skill in the art could substituted one known element for another, and the results of the substitution would have been predictable; and
- (4) whatever additional findings based on the *Graham* factual inquiries may be necessary, in view of the facts of the case under consideration, to explain a conclusion of obviousness.

If any of these findings cannot be made, then this rationale is unavailable to validate a conclusion that the claim(s) in question would have been obvious, within the meaning of Section 103.

In the present instance, the Examiner has not established any predictability, *i.e.*, at the time of filing, how one skilled in the art could predict that a stable nanoparticulate triamcinolone composition could be made. Instead, the Examiner states that nimesulide and triamcinolone are "known equivalents." Final Office Action, page 23, lines 6-9.

Second, contrary to the Examiner's contention, nimesulide and triamcinolone are NOT "known equivalents." Although both nimesulide and triamcinolone have anti-inflammation activity, the former belongs to the family of a non-steroidal anti-inflammatory drug; whereas the latter belongs to the family of corticosteroid. The chemical structures of triamcinolone and nimesulide are compared below:



Third, the Examiner's assertion of simple substitution directly contravenes the explicit teaching of the present application that "not every combination of surface stabilizer and active agent will result in a stable nanoparticulate active agent composition" (page 16, paragraph [0049]). This unpredictability in obtaining a stable nanoparticulate active agent composition is also evidenced by the teaching of Liversidge. *See the Liversidge*, for example, column 7, lines 21-23 and columns 14-15, Comparative Examples A-F.

In the absence of a detailed analysis to set forth structural similarity between triamcinolone and nimesulide, the Examiner has failed to establish that one skilled in the art would have considered it obvious to make a simple substitution. A desire of achieving enhanced bioavailability does not have any weight on the predictability that such nanoparticulate triamcinolone compositions can be obtained.

XVII. Rejection 17

The Examiner asserts that the pending claims are obvious over claims of copending Application No. 10/317,948 (the '948 application) directed to nanoparticulate compositions comprising 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methylmorpholine, which is a tachykinin receptor antagonist.

As discussed in the foregoing section, the Examiner has failed to articulate any structural or functional similarities between triamcinolone and 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methylmorpholine such that one skilled in the art would have considered it obvious to make a simple substitution. A desire of achieving enhanced bioavailability does not have any weight on the predictability that such nanoparticulate triamcinolone compositions can be obtained.

XVIII. Rejection 18

The present application was filed on October 31, 2003, whereas Application No. 11/928,250 was later filed on October 30, 2007. As discussed *supra*, filing of a terminal disclaimer is not required in an earlier filed application to overcome a provisional nonstatutory obviousness-type double patenting rejection.

XIX. Rejection 19

The present application was filed on October 31, 2003, whereas Application No. 11/367,716 was later filed on March 6, 2006. As discussed *supra*, filing of a terminal disclaimer is not required in an earlier filed application to overcome a provisional nonstatutory obviousness-type double patenting rejection.

XX. Rejection 20

The present application was filed on October 31, 2003, whereas Application No. 10/784,900 was later filed on February 24, 2004. As discussed *supra*, filing of a terminal disclaimer is not required in an earlier filed application to overcome a provisional nonstatutory obviousness-type double patenting rejection.

XXI. Rejection 21

The Examiner asserts that the claimed invention is obvious over Liversidge in view of Desai because although Liversidge does not explicitly teach triamcinolone as the corticosteroid, Desai discloses triamcinolone as an exemplary corticosteroid. Despite Appellants' arguments that Desai has no teaching to select triamcinolone as the active agent out of a long list of compounds, the Examiner insists that Desai specifically teaches triamcinolone. *See* final Office Action, the paragraph bridging pages 5-7.

A. Prior-art disclosure of a genus does not render the claimed species obvious.

Liversidge describes particles consisting essentially of a crystalline drug substance having a surface modifier adsorbed on the surface of the drug particles to maintain an effective average drug particle size of less than 400 nm. *See* abstract. Liversidge further discloses over 40 categories of drugs, but does not explicitly mention triamcinolone, which is required by the claimed invention. *See* Liversidge, column 3, line 53, through column 4, line 14. The Examiner relies on Desai for the alleged teaching of "suitable drugs includ[ing] corticosteroids such as triamcinolone acetonide" (final Office Action, page 6, lines 2-3).

Even following the Examiner's rationale, to obtain the claimed composition in view of the combined teachings of Liversidge and Desai, one skilled in the art first has to choose the drug category of corticosteroids out of 40 categories of drugs disclosed by Liversidge and the numerous drugs disclosed by Desai spanning two pages, and then among all corticosteroids, select triamcinolone. Neither of the cited references provides any guidance to make the specific selection, as the Examiner suggests.

MPEP 2144.08 requires the Examiner to consider the following aspects, where applicable:

- (a) consider the size of the genus;
- (b) consider the express teachings;
- (c) consider the teachings of structural similarity;
- (d) consider the teachings of similar properties or uses;
- (e) consider the predictability of the technology; and
- (f) consider any other teaching to support the selection of the species or subgenus.

Concerning point (a), in addition to Liversidge's disclosure of over 40 categories of drugs without an explicit disclosure of triamcinolone, Desai describes an enormous number of water insoluble pharmacologically active agents, spanning columns 11-14. Neither reference has any suggestion to preferentially select triamcinolone or the drug category that it belongs to.

In relation to point (b), Liversidge does not disclose triamcinolone, let alone any express teaching of selecting triamcinolone as the active agent. Desai lacks any express teaching of selecting triamcinolone as triamcinolone is buried in a 2-page long compound list. Therefore,

one skilled in the art would not have had any reason to select triamcinolone as the active agent to obtain the claimed composition in view of the cited references.

Turning to points (c) and (d), the over 40 categories of drugs described by Liversidge and the numerous compounds disclosed by Desai do not necessarily share any structural similarity or have similar properties or uses.

Concerning point (e), the Examiner has not yet established predictability in the art, *i.e.*, that a stable nanoparticulate composition of a particular active agent can be successfully obtained. In fact, Liversidge explicitly teaches that not every combination of active agent and surface stabilizer can produce a stable nanoparticulate active agent composition (column 7, lines 21-23, comparative examples A-F).

Finally, concerning point (f), the Examiner attempts to rely on the teaching of Desai to lead to the selection of the claimed species. Nevertheless, Desai lacks any teaching of selecting triamcinolone as the active agent out of an enormous number of the active agents. Therefore, selecting the claimed active agent, triamcinolone, in view of Desai's teaching, is no different from finding a needle in a haystack, with the Examiner's impermissible hindsight functioning as the laser pointer.

This point has been affirmed by *Takeda Chemical Industries v. Alphapharm Pty.* 492 F.3d 1350 (Fed. Cir. 2007). In *Takeda*, the prior art discloses "hundreds of millions of TZD compounds" and specifically identifies fifty-four compounds, including compound b. The court found it non-obvious to select compound b, however, because there was no indication in the prior art to show that compound b fell in the group of "the best performing compounds." *Id.* at 1357.

B. A rejection based on the "obvious-to-try" rationale must be supported by a reasonable expectation of success.

In view of the foregoing, the Examiner at most is relying on the rationale of "obvious to try" to obtain a nanoparticulate composition comprising triamcinolone. However, in view of the

Supreme Court decision in *KSR International Co. v. Teleflex Inc.*, 127 S.Ct. 1727 (2007), to substantiate an “obvious-to-try” rationale, the Examiner is required to articulate a finding that one of ordinary skill in the art could have pursued the known potential solutions with a reasonable expectation of success in obtaining the claimed invention. It has not been established that one skilled in the art would have a reasonable expectation that a stable nanoparticulate composition comprising triamcinolone can be obtained in view of the lack of predictability in the art.

Furthermore, the Examiner appears to claim that Desai compensates for the deficiency of Liversidge because Desai explicitly identifies triamcinolone as an exemplary corticosteroid. In fact, Desai lists a number of corticosteroids, such as “triamcinolone, betamethasone, betamethasone sodium phosphate, dexamethasone, dexamethasone sodium phosphate, dexamethasone acetate, prednisone, methylprednisolone acetate suspension, triamcinolone acetonide, methylprednisolone, prednisolone sodium phosphate methylprednisolone sodium succinate, hydrocortisone sodium succinate, methylprednisolone sodium succinate, triamcinolone hexacetonide, hydrocortisone, hydrocortisone cypionate, prednisolone, fluorocortisone acetate, paramethasone acetate, prednisolone tebulate, prednisolone acetate, prednisolone sodium phosphate, hydrocortisone sodium succinate” (column 14, lines 13-25). Even if one skilled in the art has any reason to select the subgenus of corticosteroid given the teaching of Liversidge, there is still an absence of guidance to select triamcinolone out of the numerous members of corticosteroids taught by Desai. The court expressly rejects the notion to try each and every member of the subgenus to obtain the claimed invention. “To vary all parameters or try each of numerous possible choices until one possibly arrive[s] at a successful result” is deemed an improper “obvious-to-try” rationale. *In re Kubin*, 561 F.3d 1351, 1359 (Fed. Cir 2009).

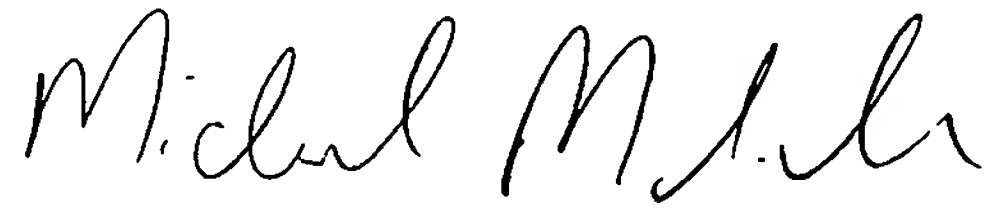
CONCLUSION

For the reasons discussed above, Appellants respectfully submit that all pending claims are in condition for allowance, and respectfully requests that the rejections be reversed in whole, and that the claims be allowed to issue.

Respectfully submitted,

Date: March 15, 2010

FOLEY & LARDNER LLP
Customer Number: 31049
Telephone: (202) 672-5538
Facsimile: (202) 672-5399

By _____

Michele M. Simkin
Attorney for Applicant
Registration No. 34,717

APPENDIX A: CLAIMS INVOLVED IN APPEAL

1. (Previously Presented) A composition comprising:
 - (a) particles of at least one triamcinolone or a salt thereof, wherein the triamcinolone particles have an effective average particle size of less than about 2000 nm and have a phase selected from the group consisting of crystalline, amorphous, and semi-crystalline; and
 - (b) at least one surface stabilizer adsorbed on the surface of the triamcinolone particles, wherein said surface stabilizer is a surfactant.
2. (Original) The composition of claim 1, wherein the triamcinolone is selected from the group consisting of triamcinolone, triamcinolone acetonide, triamcinolone diacetate, triamcinolone hexacetonide, and triamcinolone benetonide.
3. (Original) The composition of claim 2, wherein the triamcinolone is triamcinolone acetonide.
4. (Cancelled)
5. (Original) The composition of claim 1, wherein the effective average particle size of the triamcinolone particles is selected from the group consisting of less than about 1900 nm, less than about 1800 nm, less than about 1700 nm, less than about 1600 nm, less than about 1500 nm, less than about 1400 nm, less than about 1300 nm, less than about 1200 nm, less than about 1100 nm, less than about 1000 nm, less than about 900 nm, less than about 800 nm, less than about 700 nm, less than about 600 nm, less than about 500 nm, less than about 400 nm, less than about 300 nm, less than about 250 nm, less than about 200 nm, less than about 100 nm, less than about 75 nm, and less than about 50 nm.
6. (Original) The composition of claim 1, wherein the composition is formulated for administration selected from the group consisting of oral, pulmonary, rectal, ophthalmic, colonic,

parenteral, intracisternal, intravaginal, intraperitoneal, local, buccal, nasal, and topical administration.

7. (Original) The composition of claim 1 formulated into a dosage form selected from the group consisting of liquid dispersions, sachets, lozenges, oral suspensions, gels, aerosols, ointments, creams, tablets, capsules, and powders.

8. (Withdrawn) The composition of claim 1 formulated into a dosage form selected from the group consisting of controlled release formulations, fast melt formulations, lyophilized formulations, delayed release formulations, extended release formulations, pulsatile release formulations, and mixed immediate release and controlled release formulations.

9. (Original) The composition of claim 1, wherein the composition further comprises one or more pharmaceutically acceptable excipients, carriers, or a combination thereof.

10. (Original) The composition of claim 1, wherein the triamcinolone or a salt thereof is present in an amount selected from the group consisting of from about 99.5% to about 0.001%, from about 95% to about 0.1%, and from about 90% to about 0.5%, by weight, based on the total combined dry weight of the triamcinolone or salt thereof and at least one surface stabilizer, not including other excipients.

11. (Original) The composition of claim 1, wherein the at least one surface stabilizer is present in an amount selected from the group consisting of from about 0.5% to about 99.999% by weight, from about 5.0% to about 99.9% by weight, and from about 10% to about 99.5% by weight, based on the total combined dry weight of the triamcinolone or salt thereof and at least one surface stabilizer, not including other excipients.

12. (Original) The composition of claim 1, comprising at least two surface stabilizers.

13. (Previously Presented) The composition of claim 1, wherein the surface stabilizer is selected from the group consisting of a nonionic surface stabilizer, an anionic surface stabilizer, a cationic surface stabilizer, and a zwitterionic surface stabilizer.

14. (Previously Presented) The composition of claim 13, wherein the at least one surface stabilizer is selected from the group consisting of cetyl pyridinium chloride, gelatin, casein, phosphatides, dextran, glycerol, gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glycerol monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers, polyoxyethylene castor oils, polyoxyethylene sorbitan fatty acid esters, polyethylene glycols, dodecyl trimethyl ammonium bromide, polyoxyethylene stearates, colloidal silicon dioxide, phosphates, sodium dodecylsulfate, carboxymethylcellulose calcium, hydroxypropyl celluloses, hypromellose, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hypromellose phthalate, noncrystalline cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol, polyvinylpyrrolidone, 4-(1,1,3,3-tetramethylbutyl)-phenol polymer with ethylene oxide and formaldehyde, poloxamers; poloxamines, a charged phospholipid, dioctylsulfosuccinate, dialkylesters of sodium sulfosuccinic acid, sodium lauryl sulfate, alkyl aryl polyether sulfonates, mixtures of sucrose stearate and sucrose distearate, p-isononylphenoxypoly-(glycidol), decanoyl-N-methylglucamide; n-decyl β -D-glucopyranoside; n-decyl β -D-maltopyranoside; n-dodecyl β -D-glucopyranoside; n-dodecyl β -D-maltoside; heptanoyl-N-methylglucamide; n-heptyl- β -D-glucopyranoside; n-heptyl β -D-thioglucoside; n-hexyl β -D-glucopyranoside; nonanoyl-N-methylglucamide; n-nonyl β -D-glucopyranoside; octanoyl-N-methylglucamide; n-octyl- β -D-glucopyranoside; octyl β -D-thioglucopyranoside; lysozyme, PEG-phospholipid, PEG-cholesterols, PEG-vitamin A, and random copolymers of vinyl acetate and vinyl pyrrolidone.

15. (Withdrawn) The composition of claim 13, wherein the at least one cationic surface stabilizer is selected from the group consisting of a polymer, a biopolymer, a polysaccharide, a cellulosic, an alginate, a nonpolymeric compound, and a phospholipid.

16. (Withdrawn) The composition of claim 13, wherein the surface stabilizer is selected from the group consisting of cationic lipids, polymethylmethacrylate trimethylammonium bromide, sulfonium compounds, polyvinylpyrrolidone-2-dimethylaminoethyl methacrylate dimethyl sulfate, hexadecyltrimethyl ammonium bromide, phosphonium compounds, quarternary ammonium compounds, benzyl-di(2-chloroethyl)ethylammonium bromide, coconut trimethyl ammonium chloride, coconut trimethyl ammonium bromide, coconut methyl dihydroxyethyl ammonium chloride, coconut methyl dihydroxyethyl ammonium bromide, decyl triethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride bromide, C₁₂₋₁₅dimethyl hydroxyethyl ammonium chloride, C₁₂₋₁₅dimethyl hydroxyethyl ammonium chloride bromide, coconut dimethyl hydroxyethyl ammonium chloride, coconut dimethyl hydroxyethyl ammonium bromide, myristyl trimethyl ammonium methyl sulphate, lauryl dimethyl benzyl ammonium chloride, lauryl dimethyl benzyl ammonium bromide, lauryl dimethyl (ethenoxy)₄ ammonium chloride, lauryl dimethyl (ethenoxy)₄ ammonium bromide, N-alkyl (C₁₂₋₁₈)dimethylbenzyl ammonium chloride, N-alkyl (C₁₄₋₁₈)dimethyl-benzyl ammonium chloride, N-tetradecylidmethylbenzyl ammonium chloride monohydrate, dimethyl didecyl ammonium chloride, N-alkyl and (C₁₂₋₁₄) dimethyl 1-naphthylmethyl ammonium chloride, trimethylammonium halide, alkyl-trimethylammonium salts, dialkyl-dimethylammonium salts, lauryl trimethyl ammonium chloride, ethoxylated alkyamidoalkyldialkylammonium salt, an ethoxylated trialkyl ammonium salt, dialkylbenzene dialkylammonium chloride, N-didecyldimethyl ammonium chloride, N-tetradecyldimethylbenzyl ammonium, chloride monohydrate, N-alkyl(C₁₂₋₁₄) dimethyl 1-naphthylmethyl ammonium chloride, dodecyldimethylbenzyl ammonium chloride, dialkyl benzenealkyl ammonium chloride, lauryl trimethyl ammonium chloride, alkylbenzyl methyl ammonium chloride, alkyl benzyl dimethyl ammonium bromide, C₁₂ trimethyl ammonium bromides, C₁₅ trimethyl ammonium bromides, C₁₇ trimethyl ammonium bromides, dodecylbenzyl triethyl ammonium chloride, poly-diallyldimethylammonium chloride (DADMAC), dimethyl ammonium chlorides,

alkyldimethylammonium halogenides, tricetyl methyl ammonium chloride, decyltrimethylammonium bromide, dodecyltriethylammonium bromide, tetradecyltrimethylammonium bromide, methyl trioctylammonium chloride, polyquaternium 10, tetrabutylammonium bromide, benzyl trimethylammonium bromide, choline esters, benzalkonium chloride, stearalkonium chloride compounds, cetyl pyridinium bromide, cetyl pyridinium chloride, halide salts of quaternized polyoxyethylalkylamines, quaternized ammonium salt polymers, alkyl pyridinium salts; amines, amine salts, amine oxides, imide azolinium salts, protonated quaternary acrylamides, methylated quaternary polymers, and cationic guar.

17. (Original) The composition of claim 1, comprising as a surface stabilizer a random copolymer of vinyl pyrrolidone and vinyl acetate, sodium lauryl sulfate, lysozyme, tyloxapol, or a combination thereof.

18. (Previously Presented) The composition of claim 13, wherein the composition is bioadhesive.

19. (Original) The composition of claim 1, further comprising at least one additional triamcinolone composition having an effective average particle size which is different than the effective average particle size of the triamcinolone composition of claim 1.

20. (Original) The composition of claim 1, additionally comprising one or more non-triamcinolone active agents.

21. (Original) The composition of claim 20, wherein said additional one or more non-triamcinolone active agents are selected from the group consisting of nutraceuticals, amino acids, proteins, peptides, nucleotides, anti-obesity drugs, central nervous system stimulants, carotenoids, corticosteroids, elastase inhibitors, anti-fungals, oncology therapies, anti-emetics, analgesics, cardiovascular agents, anti-inflammatory agents, anthelmintics, anti-arrhythmic agents, antibiotics, anticoagulants, antidepressants, antidiabetic agents, antiepileptics,

antihistamines, antihypertensive agents, antimuscarinic agents, antimycobacterial agents, antineoplastic agents, immunosuppressants, antithyroid agents, antiviral agents, anxiolytics, sedatives, astringents, alpha-adrenergic receptor blocking agents, beta-adrenoceptor blocking agents, blood products, blood substitutes, cardiac inotropic agents, contrast media, corticosteroids, cough suppressants, decongestants, diagnostic agents, diagnostic imaging agents, diuretics, dopaminergics, haemostatics, immunological agents, lipid regulating agents, muscle relaxants, parasympathomimetics, parathyroid calcitonin, parathyroid biphosphonates, prostaglandins, radio-pharmaceuticals, sex hormones, anti-allergic agents, stimulants, anoretics, sympathomimetics, thyroid agents, vasodilators, and xanthines.

22. (Original) The composition of claim 20, wherein said additional one or more non-triamcinolone active agents are selected from the group consisting of acyclovir, alprazolam, altretamine, amiloride, amiodarone, benztropine mesylate, bupropion, cabergoline, candesartan, cerivastatin, chlorpromazine, ciprofloxacin, cisapride, clarithromycin, clonidine, clopidogrel, cyclobenzaprine, cyproheptadine, delavirdine, desmopressin, diltiazem, dipyridamole, dolasetron, enalapril maleate, enalaprilat, famotidine, felodipine, furazolidone, glipizide, irbesartan, ketoconazole, lansoprazole, loratadine, loxapine, mebendazole, mercaptopurine, milrinone lactate, minocycline, mitoxantrone, nelfinavir mesylate, nimodipine, norfloxacin, olanzapine, omeprazole, penciclovir, pimozide, tacolimus, quazepam, raloxifene, rifabutin, rifampin, risperidone, rizatriptan, saquinavir, sertraline, sildenafil, acetyl-sulfisoxazole, temazepam, thiabendazole, thioguanine, trandolapril, triamterene, trimetrexate, troglitazone, trovafloxacin, verapamil, vinblastine sulfate, mycophenolate, atovaquone, atovaquone, proguanil, ceftazidime, cefuroxime, etoposide, terbinafine, thalidomide, fluconazole, amsacrine, dacarbazine, teniposide, and acetylsalicylate.

23. (Withdrawn) The composition of claim 20, further comprising at least one antihistamine, decongestant, bronchodilator, anti-fungal, anti-cancer agent, or immunosuppressant.

24. (Withdrawn) The composition of claim 23, wherein the antihistamine is selected from the group consisting of fexofenadine, azelastine, hydroxyzine, diphenhydramine, loratadine, chlorpheniramine maleate, cyproheptadine, promethazine, phenylephrine tannate, acrivastine, and cetirizine.

25. (Withdrawn) The composition of claim 23, wherein the decongestant is selected from the group consisting of pseudoephedrine, oxymetazoline, xylometazoline, naphazoline, naphazoline, and tetrahydrozoline.

26. (Withdrawn) The composition of claim 23, wherein the bronchodilator is selected from the group consisting of short-acting beta2-agonists, long-acting beta2-agonists, anticholinergics, and theophyllines.

27. (Withdrawn) The composition of claim 23, wherein the anti-fungal agent is selected from the group consisting of amphotericin B, nystatin, fluconazole, ketoconazole, terbinafine, itraconazole, imidazole, triazole, ciclopirox, clotrimazole, and miconazole.

28. (Original) The composition of claim 1, wherein upon administration to a mammal the triamcinolone particles redisperse such that the particles have an effective average particle size of less than about 2 microns.

29. (Original) The composition of claim 28, wherein upon administration the composition redisperses such that the triamcinolone particles have an effective average particle size selected from the group consisting of less than about 1900 nm, less than about 1800 nm, less than about 1700 nm, less than about 1600 nm, less than about 1500 nm, less than about 1400 nm, less than about 1300 nm, less than about 1200 nm, less than about 1100 nm, less than about 1000 nm, less than about 900 nm, less than about 800 nm, less than about 700 nm, less than about 600 nm, less than about 500 nm, less than about 400 nm, less than about 300 nm, less than about 250 nm, less than about 200 nm, less than about 150 nm, less than about 100 nm, less than about 75 nm, and less than about 50 nm.

30. (Original) The composition of claim 1, wherein the composition redisperses in a biorelevant media such that the triamcinolone particles have an effective average particle size of less than about 2 microns.

31. (Original) The composition of claim 30, wherein the biorelevant media is selected from the group consisting of water, aqueous electrolyte solutions, aqueous solutions of a salt, aqueous solutions of an acid, aqueous solutions of a base, and combinations thereof.

32. (Original) The composition of claim 30, wherein the composition redisperses in a biorelevant media such that the triamcinolone particles have an effective average particle size selected from the group consisting of less than about 1900 nm, less than about 1800 nm, less than about 1700 nm, less than about 1600 nm, less than about 1500 nm, less than about 1400 nm, less than about 1300 nm, less than about 1200 nm, less than about 1100 nm, less than about 1000 nm, less than about 900 nm, less than about 800 nm, less than about 700 nm, less than about 600 nm, less than about 500 nm, less than about 400 nm, less than about 300 nm, less than about 250 nm, less than about 200 nm, less than about 150 nm, less than about 100 nm, less than about 75 nm, and less than about 50 nm.

33. (Original) The composition of claim 1, wherein the T_{\max} of the triamcinolone composition, when assayed in the plasma of a mammalian subject following administration, is less than the T_{\max} exhibited by a non-nanoparticulate composition of the same triamcinolone, administered at the same dosage.

34. (Original) The composition of claim 33, wherein the T_{\max} is selected from the group consisting of not greater than about 90%, not greater than about 80%, not greater than about 70%, not greater than about 60%, not greater than about 50%, not greater than about 30%, not greater than about 25%, not greater than about 20%, not greater than about 15%, not greater than about 10%, and not greater than about 5% of the T_{\max} exhibited by a non-nanoparticulate composition of the same triamcinolone, administered at the same dosage.

35. (Original) The composition of claim 1, wherein the C_{\max} of the triamcinolone composition, when assayed in the plasma of a mammalian subject following administration, is greater than the C_{\max} exhibited by a non-nanoparticulate composition of the same triamcinolone, administered at the same dosage.

36. (Original) The composition of claim 35, wherein the C_{\max} is selected from the group consisting of at least about 50%, at least about 100%, at least about 200%, at least about 300%, at least about 400%, at least about 500%, at least about 600%, at least about 700%, at least about 800%, at least about 900%, at least about 1000%, at least about 1100%, at least about 1200%, at least about 1300%, at least about 1400%, at least about 1500%, at least about 1600%, at least about 1700%, at least about 1800%, or at least about 1900% greater than the C_{\max} exhibited by a non-nanoparticulate composition of the same triamcinolone, administered at the same dosage.

37. (Original) The composition of claim 1, wherein the AUC of the triamcinolone composition, when assayed in the plasma of a mammalian subject following administration, is greater than the AUC exhibited by a non-nanoparticulate composition of the same triamcinolone, administered at the same dosage.

38. (Original) The composition of claim 37, wherein the AUC is selected from the group consisting of at least about 25%, at least about 50%, at least about 75%, at least about 100%, at least about 125%, at least about 150%, at least about 175%, at least about 200%, at least about 225%, at least about 250%, at least about 275%, at least about 300%, at least about 350%, at least about 400%, at least about 450%, at least about 500%, at least about 550%, at least about 600%, at least about 750%, at least about 700%, at least about 750%, at least about 800%, at least about 850%, at least about 900%, at least about 950%, at least about 1000%, at least about 1050%, at least about 1100%, at least about 1150%, or at least about 1200% greater than the AUC exhibited by a non-nanoparticulate composition of the same triamcinolone, administered at the same dosage.

39. (Previously Presented) The composition of claim 1, wherein when the composition is administered to a subject under fed conditions, the absorption levels of the at least one triamcinolone are substantially the same as compared to when the composition is administered to a patient under fasting conditions.

40. (Original) The composition of claim 39, wherein the difference in absorption of the triamcinolone composition of the invention, when administered in the fed versus the fasted state, is selected from the group consisting of less than about 100%, less than about 90%, less than about 80%, less than about 70%, less than about 60%, less than about 50%, less than about 40%, less than about 30%, less than about 25%, less than about 20%, less than about 15%, less than about 10%, less than about 5%, and less than about 3%.

41. (Previously Presented) The composition of claim 1, wherein administration of the composition to a subject in a fasted state is bioequivalent to administration of the composition in a fed state, wherein bioequivalency is established by a 90% Confidence Interval of between 0.80 and 1.25 for AUC and a 90% Confidence Interval of between 0.7 to 1.43 for C_{\max} .

42. (Cancelled)

43. (Previously Presented) The composition of claim 41, wherein bioequivalency is established by a 90% confidence Interval of between 0.80 and 1.25 for AUC and a 90% confidence Interval of between 0.70 to 1.43 for C_{\max} .

44. (Original) The composition of claim 1 formulated into a liquid dosage form, wherein the dosage form has a viscosity of less than about 2000 mPa·s, measured at 20°C, at a shear rate of 0.1 (1/s).

45. (Original) The composition of claim 44, having a viscosity at a shear rate of 0.1 (1/s), measured at 20°C, selected from the group consisting of from about 2000 mPa·s to about 1 mPa·s, from about 1900 mPa·s to about 1 mPa·s, from about 1800 mPa·s to about 1 mPa·s, from

about 1700 mPa·s to about 1 mPa·s, from about 1600 mPa·s to about 1 mPa·s, from about 1500 mPa·s to about 1 mPa·s, from about 1400 mPa·s to about 1 mPa·s, from about 1300 mPa·s to about 1 mPa·s, from about 1200 mPa·s to about 1 mPa·s, from about 1100 mPa·s to about 1 mPa·s, from about 1000 mPa·s to about 1 mPa·s, from about 900 mPa·s to about 1 mPa·s, from about 800 mPa·s to about 1 mPa·s, from about 700 mPa·s to about 1 mPa·s, from about 600 mPa·s to about 1 mPa·s, from about 500 mPa·s to about 1 mPa·s, from about 400 mPa·s to about 1 mPa·s, from about 300 mPa·s to about 1 mPa·s, from about 200 mPa·s to about 1 mPa·s, from about 175 mPa·s to about 1 mPa·s, from about 150 mPa·s to about 1 mPa·s, from about 125 mPa·s to about 1 mPa·s, from about 100 mPa·s to about 1 mPa·s, from about 75 mPa·s to about 1 mPa·s, from about 50 mPa·s to about 1 mPa·s, from about 25 mPa·s to about 1 mPa·s, from about 15 mPa·s to about 1 mPa·s, from about 10 mPa·s to about 1 mPa·s, and from about 5 mPa·s to about 1 mPa·s.

46. (Original) The composition of claim 44, wherein the viscosity of the dosage form is selected from the group consisting of less than about 1/200, less than about 1/100, less than about 1/50, less than about 1/25, and less than about 1/10 of the viscosity of a liquid dosage form of a non-nanoparticulate composition of the same triamcinolone, at about the same concentration per ml of triamcinolone.

47. (Original) The composition of claim 44, wherein the viscosity of the dosage form is selected from the group consisting of less than about 5%, less than about 10%, less than about 15%, less than about 20%, less than about 25%, less than about 30%, less than about 35%, less than about 40%, less than about 45%, less than about 50%, less than about 55%, less than about 60%, less than about 65%, less than about 70%, less than about 75%, less than about 80%, less than about 85%, and less than about 90% of the viscosity of a liquid dosage form of a non-nanoparticulate composition of the same triamcinolone, at about the same concentration per ml of triamcinolone.

48. (Withdrawn) A method of making a triamcinolone composition comprising contacting particles of a triamcinolone or a salt thereof with at least one surface stabilizer for a time and under conditions sufficient to provide a triamcinolone composition having an effective average particle size of less than about 2000 nm.

49. (Withdrawn) The method of claim 48, wherein the triamcinolone is selected from the group consisting of triamcinolone, triamcinolone acetonide, triamcinolone diacetate, triamcinolone hexacetonide, and triamcinolone benetonide.

50. (Withdrawn) The method of claim 49, wherein the triamcinolone is triamcinolone acetonide.

51. (Withdrawn) The method of claim 48, wherein said contacting comprises grinding.

52. (Withdrawn) The method of claim 51, wherein said grinding comprises wet grinding.

53. (Withdrawn) The method of claim 48, wherein said contacting comprises homogenizing.

54. (Withdrawn) The method of claim 48, wherein said contacting comprises:

- (a) dissolving the particles of a triamcinolone or salt thereof in a solvent;
- (b) adding the resulting triamcinolone solution to a solution comprising at least one surface stabilizer; and
- (c) precipitating the solubilized triamcinolone/surface stabilizer composition by the addition of a non-solvent.

55. (Withdrawn) The method of claim 48, wherein the triamcinolone or salt thereof is selected from the group consisting of a crystalline phase, an amorphous phase, a semi-crystalline phase, a semi-amorphous phase, and mixtures thereof.

56. (Withdrawn) The method of claim 48, wherein the effective average particle size of the triamcinolone particles is selected from the group consisting of less than about 1900 nm, less than about 1800 nm, less than about 1700 nm, less than about 1600 nm, less than about 1500 nm, less than about 1000 nm, less than about 1400 nm, less than about 1300 nm, less than about 1200 nm, less than about 1100 nm, less than about 900 nm, less than about 800 nm, less than about 700 nm, less than about 600 nm, less than about 500 nm, less than about 400 nm, less than about 300 nm, less than about 250 nm, less than about 200 nm, less than about 100 nm, less than about 75 nm, and less than about 50 nm.

57. (Withdrawn) The method of claim 48, wherein the triamcinolone or salt thereof is present in an amount selected from the group consisting of from about 99.5% to about 0.001%, from about 95% to about 0.1%, and from about 90% to about 0.5%, by weight, based on the total combined dry weight of the triamcinolone or a salt thereof and at least one surface stabilizer, not including other excipients.

58. (Withdrawn) The method of claim 48, wherein the at least one surface stabilizer is present in an amount selected from the group consisting of from about 0.5% to about 99.999%, from about 5.0% to about 99.9%, and from about 10% to about 99.5% by weight, based on the total combined dry weight of the triamcinolone or a salt thereof and at least one surface stabilizer, not including other excipients.

59. (Withdrawn) The method of claim 48, utilizing at least two surface stabilizers.

60. (Withdrawn) The method of claim 48, wherein the surface stabilizer is selected from the group consisting of a nonionic surface stabilizer, an anionic surface stabilizer, a cationic surface stabilizer, a zwitterionic surface stabilizer, and an ionic surface stabilizer.

61. (Withdrawn) The method of claim 60, wherein the at least one surface stabilizer is selected from the group consisting of cetyl pyridinium chloride, gelatin, casein, phosphatides, dextran, glycerol, gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glycerol monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers, polyoxyethylene castor oils, polyoxyethylene sorbitan fatty acid esters, polyethylene glycols, dodecyl trimethyl ammonium bromide, polyoxyethylene stearates, colloidal silicon dioxide, phosphates, sodium dodecylsulfate, carboxymethylcellulose calcium, hydroxypropyl celluloses, hypromellose, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hypromellose phthalate, noncrystalline cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol, polyvinylpyrrolidone, 4-(1,1,3,3-tetramethylbutyl)-phenol polymer with ethylene oxide and formaldehyde, poloxamers; poloxamines, a charged phospholipid, dioctylsulfosuccinate, dialkylesters of sodium sulfosuccinic acid, sodium lauryl sulfate, alkyl aryl polyether sulfonates, mixtures of sucrose stearate and sucrose distearate, p-isononylphenoxypoly-(glycidol), decanoyl-N-methylglucamide; n-decyl β -D-glucopyranoside; n-decyl β -D-maltopyranoside; n-dodecyl β -D-glucopyranoside; n-dodecyl β -D-maltoside; heptanoyl-N-methylglucamide; n-heptyl- β -D-glucopyranoside; n-heptyl β -D-thioglucoside; n-hexyl β -D-glucopyranoside; nonanoyl-N-methylglucamide; n-nonyl β -D-glucopyranoside; octanoyl-N-methylglucamide; n-octyl- β -D-glucopyranoside; octyl β -D-thioglucopyranoside; lysozyme, PEG-phospholipid, PEG-cholesterols, PEG-vitamin A, PEG-vitamin E, and random copolymers of vinyl acetate and vinyl pyrrolidone.

62. (Withdrawn) The method of claim 60, wherein the at least one cationic surface stabilizer is selected from the group consisting of a polymer, a biopolymer, a polysaccharide, a cellulosic, an alginate, a nonpolymeric compound, and a phospholipid.

63. (Withdrawn) The method of claim 60, wherein the surface stabilizer is selected from the group consisting of cationic lipids, polymethylmethacrylate trimethylammonium

bromide, sulfonium compounds, polyvinylpyrrolidone-2-dimethylaminoethyl methacrylate dimethyl sulfate, hexadecyltrimethyl ammonium bromide, phosphonium compounds, quaternary ammonium compounds, benzyl-di(2-chloroethyl)ethylammonium bromide, coconut trimethyl ammonium chloride, coconut trimethyl ammonium bromide, coconut methyl dihydroxyethyl ammonium chloride, coconut methyl dihydroxyethyl ammonium bromide, decyl triethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride bromide, C₁₂₋₁₅dimethyl hydroxyethyl ammonium chloride, C₁₂₋₁₅dimethyl hydroxyethyl ammonium chloride bromide, coconut dimethyl hydroxyethyl ammonium chloride, coconut dimethyl hydroxyethyl ammonium bromide, myristyl trimethyl ammonium methyl sulphate, lauryl dimethyl benzyl ammonium chloride, lauryl dimethyl benzyl ammonium bromide, lauryl dimethyl (ethenoxy)₄ ammonium chloride, lauryl dimethyl (ethenoxy)₄ ammonium bromide, N-alkyl (C₁₂₋₁₈)dimethylbenzyl ammonium chloride, N-alkyl (C₁₄₋₁₈)dimethyl-benzyl ammonium chloride, N-tetradecyldimethylbenzyl ammonium chloride monohydrate, dimethyl didecyl ammonium chloride, N-alkyl and (C₁₂₋₁₄) dimethyl 1-naphthylmethyl ammonium chloride, trimethylammonium halide, alkyl-trimethylammonium salts, dialkyl-dimethylammonium salts, lauryl trimethyl ammonium chloride, ethoxylated alkyamidoalkyldialkylammonium salt, an ethoxylated trialkyl ammonium salt, dialkylbenzene dialkylammonium chloride, N-didecyldimethyl ammonium chloride, N-tetradecyldimethylbenzyl ammonium, chloride monohydrate, N-alkyl(C₁₂₋₁₄) dimethyl 1-naphthylmethyl ammonium chloride, dodecyldimethylbenzyl ammonium chloride, dialkyl benzenealkyl ammonium chloride, lauryl trimethyl ammonium chloride, alkylbenzyl methyl ammonium chloride, alkyl benzyl dimethyl ammonium bromide, C₁₂ trimethyl ammonium bromides, C₁₅ trimethyl ammonium bromides, C₁₇ trimethyl ammonium bromides, dodecylbenzyl triethyl ammonium chloride, polydiallyldimethylammonium chloride (DADMAC), dimethyl ammonium chlorides, alkyldimethylammonium halogenides, tricetyl methyl ammonium chloride, decyltrimethylammonium bromide, dodecyltriethylammonium bromide, tetradecyltrimethylammonium bromide, methyl trioctylammonium chloride, polyquaternium 10,

tetrabutylammonium bromide, benzyl trimethylammonium bromide, choline esters, benzalkonium chloride, stearalkonium chloride compounds, cetyl pyridinium bromide, cetyl pyridinium chloride, halide salts of quaternized polyoxyethylalkylamines, quaternized ammonium salt polymers, alkyl pyridinium salts; amines, amine salts, amine oxides, imide azolinium salts, protonated quaternary acrylamides, methylated quaternary polymers, and cationic guar.

64. (Withdrawn) The composition of claim 1, comprising as a surface stabilizer a random copolymer of vinyl pyrrolidone and vinyl acetate, sodium lauryl sulfate, lysozyme, tyloxapol, or a combination thereof.

65. (Withdrawn) The method of claim 60, wherein the composition is bioadhesive.

66. (Withdrawn) A method of treating a subject in need comprising administering to the subject an effective amount of a composition comprising:

- (a) particles of a triamcinolone or a salt thereof, wherein the triamcinolone particles have an effective average particle size of less than about 2000 nm; and
- (b) at least one surface stabilizer.

67. (Withdrawn) The method of claim 66, wherein the triamcinolone is selected from the group consisting of triamcinolone, triamcinolone acetonide, triamcinolone diacetate, triamcinolone hexacetone, and triamcinolone benetonide.

68. (Withdrawn) The method of claim 67, wherein the triamcinolone is triamcinolone acetonide.

69. (Withdrawn) The method of claim 66, wherein the triamcinolone or a salt thereof is selected from the group consisting of a crystalline phase, an amorphous phase, a semi-crystalline phase, a semi-amorphous phase, and mixtures thereof.

70. (Withdrawn) The method of claim 66, wherein the effective average particle size of the triamcinolone particles is selected from the group consisting of less than about 1900 nm, less than about 1800 nm, less than about 1700 nm, less than about 1600 nm, less than about 1500 nm, less than about 1400 nm, less than about 1300 nm, less than about 1200 nm, less than about 1100 nm, less than about 1000 nm, less than about 900 nm, less than about 800 nm, less than about 700 nm, less than about 600 nm, less than about 500 nm, less than about 400 nm, less than about 300 nm, less than about 250 nm, less than about 200 nm, less than about 100 nm, less than about 75 nm, and less than about 50 nm.

71. (Withdrawn) The method of claim 66, wherein the composition is formulated for administration selected from the group consisting of oral, pulmonary, rectal, ophthalmic, colonic, parenteral, intracisternal, intravaginal, intraperitoneal, local, buccal, nasal, and topical administration.

72. (Withdrawn) The method of claim 66, wherein the composition further comprises one or more pharmaceutically acceptable excipients, carriers, or a combination thereof.

73. (Withdrawn) The method of claim 66, wherein the triamcinolone or salt thereof is present in an amount selected from the group consisting of from about 99.5% to about 0.001%, from about 95% to about 0.1%, and from about 90% to about 0.5%, by weight, based on the total combined dry weight of the triamcinolone or salt thereof and at least one surface stabilizer, not including other excipients.

74. (Withdrawn) The method of claim 66, wherein the at least one surface stabilizer is present in an amount selected from the group consisting of from about 0.5% to about 99.999% by weight, from about 5.0% to about 99.9% by weight, and from about 10% to about 99.5% by weight, based on the total combined dry weight of the triamcinolone or a salt thereof and at least one surface stabilizer, not including other excipients.

75. (Withdrawn) The method of claim 66, utilizing at least two surface stabilizers.

76. (Withdrawn) The method of claim 66, wherein at least one surface stabilizer is selected from the group consisting of a nonionic surface stabilizer, an anionic surface stabilizer, a cationic surface stabilizer, a zwitterionic surface stabilizer, and an ionic surface stabilizer.

77. (Withdrawn) The method of claim 76, wherein at least one surface stabilizer is selected from the group consisting of cetyl pyridinium chloride, gelatin, casein, phosphatides, dextran, glycerol, gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glycerol monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers, polyoxyethylene castor oils, polyoxyethylene sorbitan fatty acid esters, polyethylene glycols, dodecyl trimethyl ammonium bromide, polyoxyethylene stearates, colloidal silicon dioxide, phosphates, sodium dodecylsulfate, carboxymethylcellulose calcium, hydroxypropyl celluloses, hypromellose, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hypromellose phthalate, noncrystalline cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol, polyvinylpyrrolidone, 4-(1,1,3,3-tetramethylbutyl)-phenol polymer with ethylene oxide and formaldehyde, poloxamers; poloxamines, a charged phospholipid, dioctylsulfosuccinate, dialkylesters of sodium sulfosuccinic acid, sodium lauryl sulfate, alkyl aryl polyether sulfonates, mixtures of sucrose stearate and sucrose distearate, p-isononylphenoxypoly-(glycidol), decanoyl-N-methylglucamide; n-decyl β -D-glucopyranoside; n-decyl β -D-maltopyranoside; n-dodecyl β -D-glucopyranoside; n-dodecyl β -D-maltoside; heptanoyl-N-methylglucamide; n-heptyl- β -D-glucopyranoside; n-heptyl β -D-thioglucoside; n-hexyl β -D-glucopyranoside; nonanoyl-N-methylglucamide; n-nonyl β -D-glucopyranoside; octanoyl-N-methylglucamide; n-octyl- β -D-glucopyranoside; octyl β -D-thioglucopyranoside; lysozyme, PEG-phospholipid, PEG-cholesterols, PEG-vitamin A, PEG-vitamin E, and random copolymers of vinyl acetate and vinyl pyrrolidone.

78. (Withdrawn) The method of claim 76, wherein at least one cationic surface stabilizer is selected from the group consisting of a polymer, a biopolymer, a polysaccharide, a cellulosic, an alginate, a nonpolymeric compound, and a phospholipid.

79. (Withdrawn) The method of claim 76, wherein the surface stabilizer is selected from the group consisting of benzalkonium chloride, polymethylmethacrylate trimethylammonium bromide, polyvinylpyrrolidone-2-dimethylaminoethyl methacrylate dimethyl sulfate, hexadecyltrimethyl ammonium bromide, cationic lipids, sulfonium compounds, phosphonium compounds, quarternary ammonium compounds, benzyl-di(2-chloroethyl)ethylammonium bromide, coconut trimethyl ammonium chloride, coconut trimethyl ammonium bromide, coconut methyl dihydroxyethyl ammonium chloride, coconut methyl dihydroxyethyl ammonium bromide, decyl triethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride bromide, C₁₂₋₁₅dimethyl hydroxyethyl ammonium chloride, C₁₂₋₁₅dimethyl hydroxyethyl ammonium chloride bromide, coconut dimethyl hydroxyethyl ammonium chloride, coconut dimethyl hydroxyethyl ammonium bromide, myristyl trimethyl ammonium methyl sulphate, lauryl dimethyl benzyl ammonium chloride, lauryl dimethyl benzyl ammonium bromide, lauryl dimethyl (ethenoxy)₄ ammonium chloride, lauryl dimethyl (ethenoxy)₄ ammonium bromide, N-alkyl (C₁₂₋₁₈)dimethylbenzyl ammonium chloride, N-alkyl (C₁₄₋₁₈)dimethyl-benzyl ammonium chloride, N-tetradecyldimethylbenzyl ammonium chloride monohydrate, dimethyl didecyl ammonium chloride, N-alkyl and (C₁₂₋₁₄) dimethyl 1-naphthylmethyl ammonium chloride, trimethylammonium halide, alkyl-trimethylammonium salts, dialkyl-dimethylammonium salts, lauryl trimethyl ammonium chloride, ethoxylated alkyamidoalkyldialkylammonium salt, an ethoxylated trialkyl ammonium salt, dialkylbenzene dialkylammonium chloride, N-didecyldimethyl ammonium chloride, N-tetradecyldimethylbenzyl ammonium, chloride monohydrate, N-alkyl(C₁₂₋₁₄) dimethyl 1-naphthylmethyl ammonium chloride, dodecyldimethylbenzyl ammonium chloride, dialkyl benzenealkyl ammonium chloride, lauryl trimethyl ammonium chloride, alkylbenzyl methyl ammonium chloride, alkyl benzyl dimethyl

ammonium bromide, C₁₂ trimethyl ammonium bromides, C₁₅ trimethyl ammonium bromides, C₁₇ trimethyl ammonium bromides, dodecylbenzyl triethyl ammonium chloride, poly-diallyldimethylammonium chloride (DADMAC), dimethyl ammonium chlorides, alkyldimethylammonium halogenides, tricetyl methyl ammonium chloride, decyltrimethylammonium bromide, dodecyltriethylammonium bromide, tetradecyltrimethylammonium bromide, methyl trioctylammonium chloride, polyquaternium 10, tetrabutylammonium bromide, benzyl trimethylammonium bromide, choline esters, benzalkonium chloride, stearalkonium chloride compounds, cetyl pyridinium bromide, cetyl pyridinium chloride, halide salts of quaternized polyoxyethylalkylamines, quaternized ammonium salt polymers, alkyl pyridinium salts; amines, amine salts, amine oxides, imide azolinium salts, protonated quaternary acrylamides, methylated quaternary polymers, and cationic guar.

80. (Withdrawn) The method of claim 66, comprising as a surface stabilizer a random copolymer of vinyl pyrrolidone and vinyl acetate, sodium lauryl sulfate, lysozyme, tyloxapol, or a combination thereof.

81. (Withdrawn) The method of claim 76, wherein the composition is bioadhesive.

82. (Withdrawn) The method of claim 66, additionally comprising administering one or more non-triamcinolone active agents.

83. (Withdrawn) The method of claim 82, wherein said additional one or more non-triamcinolone active agents are selected from the group consisting of nutraceuticals, amino acids, proteins, peptides, nucleotides, anti-obesity drugs, central nervous system stimulants, carotenoids, corticosteroids, elastase inhibitors, anti-fungals, oncology therapies, anti-emetics, analgesics, cardiovascular agents, anti-inflammatory agents, anthelmintics, anti-arrhythmic agents, antibiotics, anticoagulants, antidepressants, antidiabetic agents, antiepileptics, antihistamines, antihypertensive agents, antimuscarinic agents, antimycobacterial agents,

antineoplastic agents, immunosuppressants, antithyroid agents, antiviral agents, anxiolytics, sedatives, astringents, alpha-adrenergic receptor blocking agents, beta-adrenoceptor blocking agents, blood products, blood substitutes, cardiac inotropic agents, contrast media, corticosteroids, cough suppressants, diagnostic agents, diagnostic imaging agents, diuretics, dopaminergics, haemostatics, immunological agents, lipid regulating agents, muscle relaxants, parasympathomimetics, parathyroid calcitonin, parathyroid biphosphonates, prostaglandins, radio-pharmaceuticals, sex hormones, anti-allergic agents, stimulants, anoretics, sympathomimetics, thyroid agents, vasodilators, and xanthines.

84. (Withdrawn) The method of claim 82, wherein said additional one or more non-triamcinolone active agents are selected from the group consisting of acyclovir, alprazolam, altretamine, amiloride, amiodarone, benztropine mesylate, bupropion, cabergoline, candesartan, cerivastatin, chlorpromazine, ciprofloxacin, cisapride, clarithromycin, clonidine, clopidogrel, cyclobenzaprine, cyproheptadine, delavirdine, desmopressin, diltiazem, dipyridamole, dolasetron, enalapril maleate, enalaprilat, famotidine, felodipine, furazolidone, glipizide, irbesartan, ketoconazole, lansoprazole, loratadine, loxapine, mebendazole, mercaptopurine, milrinone lactate, minocycline, mitoxantrone, nelfinavir mesylate, nimodipine, norfloxacin, olanzapine, omeprazole, penciclovir, pimozide, tacolimus, quazepam, raloxifene, rifabutin, rifampin, risperidone, rizatriptan, saquinavir, sertraline, sildenafil, acetyl-sulfisoxazole, temazepam, thiabendazole, thioguanine, trandolapril, triamterene, trimetrexate, troglitazone, trovafloxacin, verapamil, vinblastine sulfate, mycophenolate, atovaquone, atovaquone, proguanil, ceftazidime, cefuroxime, etoposide, terbinafine, thalidomide, fluconazole, amsacrine, dacarbazine, teniposide, and acetylsalicylate.

85. (Withdrawn) The method of claim 82, further comprising administering at least one antihistamine, decongestant, bronchodilator, anti-fungal, anti-cancer agent, or immunosuppressant.

86. (Withdrawn) The method of claim 85, wherein the antihistamine is selected from the group consisting of fexofenadine, azelastine, hydroxyzine, diphenhydramine, loratadine, chlorpheniramine maleate, cyproheptadine, promethazine, phenylephrine tannate, acrivastine, and cetirizine.

87. (Withdrawn) The method of claim 85, wherein the decongestant is selected from the group consisting of pseudoephedrine, oxymetazoline, xylometazoline, naphazoline, naphazoline, and tetrahydrozoline.

88. (Withdrawn) The method of claim 85, wherein the bronchodilator is selected from the group consisting of short-acting beta2-agonists, long-acting beta2-agonists, anticholinergics, and theophyllines.

89. (Withdrawn) The method of claim 85, wherein the anti-fungal agent is selected from the group consisting of amphotericin B, nystatin, fluconazole, ketoconazole, terbinafine, itraconazole, imidazole, triazole, ciclopirox, clotrimazole, and miconazole.

90. (Withdrawn) The method of claim 66, wherein the T_{\max} of the triamcinolone composition, when assayed in the plasma of a mammalian subject following administration, is less than the T_{\max} for a non-nanoparticulate composition of the same triamcinolone, administered at the same dosage.

91. (Withdrawn) The method of claim 90, wherein the T_{\max} is selected from the group consisting of not greater than about 90%, not greater than about 80%, not greater than about 70%, not greater than about 60%, not greater than about 50%, not greater than about 30%, not greater than about 25%, not greater than about 20%, not greater than about 15%, not greater than about 10%, and not greater than about 5% of the T_{\max} exhibited by the non-nanoparticulate composition of the same triamcinolone, administered at the same dosage.

92. (Withdrawn) The method of claim 66, wherein the C_{\max} of the triamcinolone composition, when assayed in the plasma of a mammalian subject following administration, is greater than the C_{\max} for a non-nanoparticulate composition of the same triamcinolone, administered at the same dosage.

93. (Withdrawn) The method of claim 92, wherein the C_{\max} is selected from the group consisting of at least about 50%, at least about 100%, at least about 200%, at least about 300%, at least about 400%, at least about 500%, at least about 600%, at least about 700%, at least about 800%, at least about 900%, at least about 1000%, at least about 1100%, at least about 1200%, at least about 1300%, at least about 1400%, at least about 1500%, at least about 1600%, at least about 1700%, at least about 1800%, or at least about 1900% greater than the C_{\max} exhibited by the non-nanoparticulate formulation of the same triamcinolone, administered at the same dosage.

94. (Withdrawn) The method of claim 66, wherein the AUC of the triamcinolone composition, when assayed in the plasma of a mammalian subject following administration, is greater than the AUC for a non-nanoparticulate composition of the same triamcinolone, administered at the same dosage.

95. (Withdrawn) The method of claim 94, wherein the AUC is selected from the group consisting of at least about 25%, at least about 50%, at least about 75%, at least about 100%, at least about 125%, at least about 150%, at least about 175%, at least about 200%, at least about 225%, at least about 250%, at least about 275%, at least about 300%, at least about 350%, at least about 400%, at least about 450%, at least about 500%, at least about 550%, at least about 600%, at least about 750%, at least about 700%, at least about 750%, at least about 800%, at least about 850%, at least about 900%, at least about 950%, at least about 1000%, at least about 1050%, at least about 1100%, at least about 1150%, or at least about 1200% greater than the AUC exhibited by the non-nanoparticulate composition of the same triamcinolone, administered at the same dosage.

96. (Withdrawn) The method of claim 66, wherein when the triamcinolone composition is administered to the subject under fed conditions, the absorption levels of the at least one triamcinolone are substantially the same as compared when the composition is administered to a patient under fasting conditions.

97. (Withdrawn) The method of claim 96, wherein the difference in absorption of the triamcinolone composition of the invention, when administered in the fed versus the fasted state, is selected from the group consisting of less than about 100%, less than about 90%, less than about 80%, less than about 70%, less than about 60%, less than about 50%, less than about 40%, less than about 30%, less than about 25%, less than about 20%, less than about 15%, less than about 10%, less than about 5%, and less than about 3%.

98. (Withdrawn) The method of claim 66, wherein administration of the composition to a human in a fasted state is bioequivalent to administration of the composition to a human in a fed state.

99. (Withdrawn) The method of claim 98, wherein “bioequivalency” is established by a 90% Confidence Interval of between 0.80 and 1.25 for both C_{\max} and AUC.

100. (Withdrawn) The method of claim 98, wherein “bioequivalency” is established by a 90% Confidence Interval of between 0.80 and 1.25 for AUC and a 90% Confidence Interval of between 0.70 to 1.43 for C_{\max} .

101. (Withdrawn) The method of claim 66, wherein the subject is a human.

102. (Withdrawn) The method of claim 66, wherein the method is used to treat indications where glucocorticoids are typically used.

103. (Withdrawn) The method of claim 66, wherein the method is used to treat indications where steroidal anti-inflammatory agents are typically used.

104. (Withdrawn) The method of claim 66, wherein the method is used to treat indications selected from the group consisting of arthritis, skin disorders, blood disorders, kidney disorders, eye disorders, thyroid disorders, intestinal disorders, allergies, asthma, bronchial asthma, cancer, neoplastic diseases, tendinitis, allergic reactions, seasonal allergic rhinitis, perennial allergic rhinitis, oral inflammation, oral lesions, oral ulcers, bursitis, epicondylitis, keloids, endocrine disorders, herpes zoster ophthalmicus, hemolytic anemia, and acute rheumatic carditis.

105. (Withdrawn) The method of claim 104, wherein the skin disorder is selected from the group consisting of contact dermatitis, atopic dermatitis, psoriasis, eczema, and general dermatitis.

106. (Withdrawn) The method of claim 104, wherein the arthritic condition is selected from the group consisting of osteoarthritis, acute nonspecific osteoarthritis, posttraumatic osteoarthritis, and rheumatoid arthritis.

107. (Withdrawn) The method of claim 104, wherein the intestinal disorder is selected from the group consisting of ulcerative colitis, colitis, gastroenteritis, irritable bowel disorder, and Crohn's disease.

108. (Withdrawn) The method of claim 66, wherein the method is used to treat indications selected from the group consisting of asthma, seasonal allergic rhinitis, and perennial allergic rhinitis.

APPENDIX B: EVIDENCE

1. U.S. Patent No. 5,145,684 to Liversidge et al.;
2. U.S. Patent No. 5,916,596 to Desai et al.;
3. Pending claims in U.S. Patent Application No. 12/320,431;
4. Pending claims in U.S. Patent Application No. 12/292,092;
5. Pending claims in U.S. Patent Application No. 12/117,982;
6. Pending claims in U.S. Patent Application No. 12/052,436;
7. Pending claims in U.S. Patent Application No. 12/051,448;
8. Pending claims in U.S. Patent Application No. 11/980,719;
9. Pending claims in U.S. Patent Application No. 11/979,253;
10. Pending claims in U.S. Patent Application No. 11/761,900;
11. Pending claims in U.S. Patent Application No. 11/436,887;
12. Pending claims in U.S. Patent Application No. 11/376,553;
13. Pending claims in U.S. Patent Application No. 11/275,069;
14. Pending claims in U.S. Patent Application No. 10/912,552;
15. Pending claims in U.S. Patent Application No. 10/895,405;
16. Pending claims in U.S. Patent Application No. 10/768,194;
17. Pending claims in U.S. Patent Application No. 10/701,064;

18. Pending claims in U.S. Patent Application No. 10/697,703;

19. Pending claims in U.S. Patent Application No. 10/317,948;

20. Pending claims in U.S. Patent Application No. 11/928, 250;

21. Pending claims in U.S. Patent Application No. 11/367,716;

22. Pending claims in U.S. Patent Application No. 10/784,900.

APPENDIX C: RELATED PROCEEDINGS

No related proceedings are pending.



US005145684A

United States Patent [19][11] Patent Number: **5,145,684**

Liversidge et al.

[45] Date of Patent: **Sep. 8, 1992**[54] **SURFACE MODIFIED DRUG
NANOPARTICLES**[75] Inventors: Gary G. Liversidge, West Chester;
Kenneth C. Cundy, Pottstown, both
of Pa.; John F. Bishop, Rochester;
David A. Czekal, Honeoye Falls,
both of N.Y.

[73] Assignee: Sterling Drug Inc., New York, N.Y.

[21] Appl. No.: 647,105

[22] Filed: Jan. 25, 1991

[51] Int. Cl.³ A61K 9/14[52] U.S. Cl. 424/489; 424/495;
424/499

[58] Field of Search 424/495, 489, 499

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Pharmacy", Chapter 2, Milling (1986).Remington's Pharmaceutical Sciences 17th Edition,
Chapter 20, Schott, H., "Colloidal Dispersions".*Primary Examiner*—Thurman K. Page*Assistant Examiner*—William E. Benston, Jr.*Attorney, Agent, or Firm*—Arthur H. Rosenstein;
William J. Davis[57] **ABSTRACT**

Dispersible particles consisting essentially of a crystal-
line drug substance having a surface modifier adsorbed
on the surface thereof in an amount sufficient to main-
tain an effective average particle size of less than about
400 nm, methods for the preparation of such particles
and dispersions containing the particles. Pharmaceutical
compositions containing the particles exhibit unex-
pected bioavailability and are useful in methods of treat-
ing mammals.

20 Claims, No Drawings



US005916596A

United States Patent [19][11] **Patent Number:** **5,916,596****Desai et al.**[45] **Date of Patent:** **Jun. 29, 1999**

[54] **PROTEIN STABILIZED
PHARMACOLOGICALLY ACTIVE AGENTS,
METHODS FOR THE PREPARATION
THEREOF AND METHODS FOR THE USE
THEREOF**

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Primary Examiner—Neil S. Levy*Assistant Examiner*—William E. Benston, Jr.*Attorney, Agent, or Firm*—Gray, Cary, Ware & Freidenrich; Stephen E. Reiter

[75] **Inventors:** Nell P. Desai, Los Angeles; Chunlin Tao, Beverly Hills; Andrew Yang, Rosemead; Leslie Louie, Montebello; Tianli Zheng; Zhiwen Yao, both of Culver City; Patrick Soon-Shiong, Los Angeles, all of Calif.; Shlomo Magdassi, Jerusalem, Israel

[73] **Assignee:** Vivorx Pharmaceuticals, Inc., Santa Monica, Calif.

[21] **Appl. No.:** 08/720,756[22] **Filed:** Oct. 1, 1996**Related U.S. Application Data**

[60] Continuation-in-part of application No. 08/412,726, Mar. 29, 1995, Pat. No. 5,560,933, which is a division of application No. 08/023,698, Feb. 22, 1993, Pat. No. 5,439,686.

[51] **Int. Cl.⁶** A61K 9/14[52] **U.S. Cl.** 424/489; 424/450; 424/465; 424/451; 424/439[58] **Field of Search** 424/489, 422, 424/423, 475, 9.1, 9.3, 9.32, 450, 400[56] **References Cited****U.S. PATENT DOCUMENTS**

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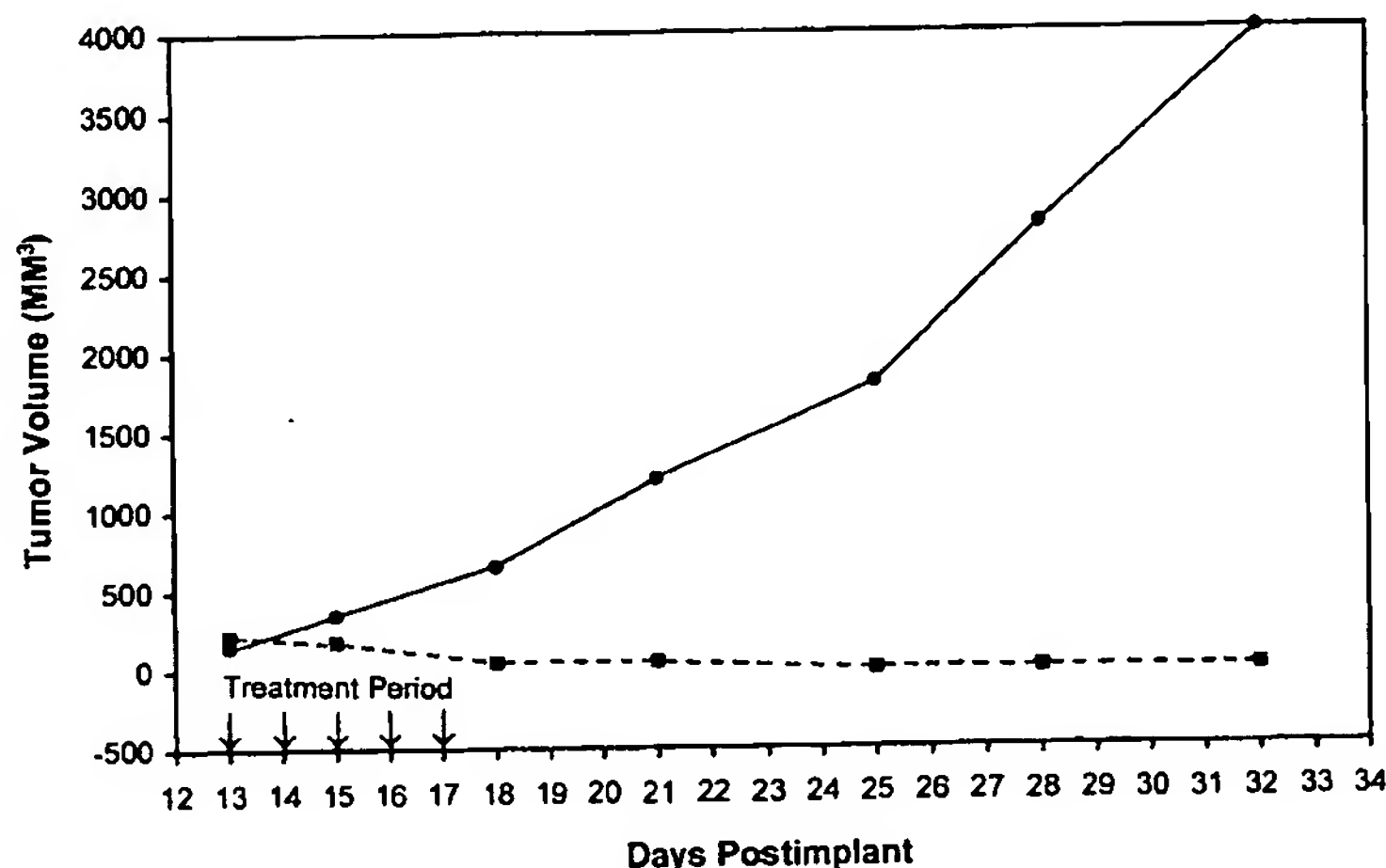
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[57] **ABSTRACT**

In accordance with the present invention, there are provided compositions and methods useful for the in vivo delivery of substantially water insoluble pharmacologically active agents (such as the anticancer drug paclitaxel) in which the pharmacologically active agent is delivered in the form of suspended particles coated with protein (which acts as a stabilizing agent). In particular, protein and pharmacologically active agent in a biocompatible dispersing medium are subjected to high shear, in the absence of any conventional surfactants, and also in the absence of any polymeric core material for the particles. The procedure yields particles with a diameter of less than about 1 micron. The use of specific composition and preparation conditions (e.g., addition of a polar solvent to the organic phase), and careful selection of the proper organic phase and phase fraction, enables the reproducible production of unusually small nanoparticles of less than 200 nm diameter, which can be sterile-filtered. The particulate system produced according to the invention can be converted into a redispersible dry powder comprising nanoparticles of water-insoluble drug coated with a protein, and free protein to which molecules of the pharmacological agent are bound. This results in a unique delivery system, in which part of the pharmacologically active agent is readily bioavailable (in the form of molecules bound to the protein), and part of the agent is present within particles without any polymeric matrix therein.

31 Claims, 2 Drawing Sheets

AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions of claims in the application.

1.-50. (Cancelled)

51. (New) A propellant-based dry powder composition for pulmonary or nasal delivery comprising nanoparticulate drug particles and at least one propellant, wherein the nanoparticulate drug particles:

- (a) comprise a poorly soluble drug in crystalline form, amorphous form, or a combination thereof;
- (b) have an effective average particle size of less than about 1000 nm, and
- (c) have at least one surface modifier adsorbed on the surface thereof.

52. (New) The composition of claim 51, wherein the nanoparticulate drug particles and the surface modifier form aggregates.

53. (New) The composition of claim 52, wherein the aggregates are less than or equal to about 100 microns in diameter.

54. (New) The composition of claim 52, wherein the aggregates have a size of from about 2 microns to about 5 microns.

55. (New) The composition of claim 51, further comprising a diluent.

56. (New) The composition of claim 55, wherein the diluent is lactose or mannitol.

57. (New) The composition of claim 55, wherein essentially every diluent particle comprises at least one embedded nanoparticulate drug particle having a surface modifier adhered to the surface of the drug particle.

58. (New) The composition of claim 51, wherein the dry powder is prepared by a method selected from the group consisting of (a) spray-drying aqueous dispersions nanoparticulate drug particles and (b) freeze-drying aqueous dispersions nanoparticulate drug particles.

59. (New) The composition of claim 51, wherein the propellant is selected from the group consisting of a chlorinated propellant, a non-chlorinated propellant, a hydrofluorinated alkane, and a halogenated hydrocarbon propellant having a low boiling point.

60. (New) The composition of claim 51, wherein the drug is selected from the group consisting of proteins, peptides, elastase inhibitors, analgesics, cystic-fibrosis therapies, asthma therapies, emphysema therapies, respiratory distress syndrome therapies, chronic bronchitis therapies, chronic obstructive pulmonary disease therapies, organ-transplant rejection therapies, therapies for tuberculosis and other infections of the lung, fungal infection therapies, and respiratory illness therapies associated with acquired immune deficiency syndrome, an oncology drug, an anti-emetic, a cardiovascular agent, beclomethasone dipropionate, naproxen, triamcinolone acetonide, budesonide, and an anti-emetic.

61. (New) The composition of claim 51, wherein the nanoparticulate drug particles have an effective average particle size selected from the group consisting of less than about 400 nm, less than about 300 nm, less than about 250 nm, less than about 100 nm, and less than about 50 nm.

62. (New) The composition of claim 51, wherein the concentration of the drug is from about 0.05 mg/g up to about 990 mg/g.

63. (New) The composition of claim 51, wherein the surface modifier is selected from the group consisting of a nonionic surfactant and an ionic surfactant.

64. (New) The composition of claim 51, wherein the surface modifier is selected from the group consisting of tyloxapol, cetyl pyridinium chloride, gelatin, casein, lecithin, dextran, glycerol, gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glycerol monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers, polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters; polyethylene glycols, dodecyl trimethyl ammonium bromide, polyoxyethylene stearates, colloidal silicon dioxide, phosphates, sodium dodecylsulfate, carboxymethylcellulose calcium, hydroxypropyl cellulose, hydroxypropyl methylcellulose, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethyl-cellulose phthalate, noncrystalline cellulose, magnesium aluminum

silicate, triethanolamine, polyvinyl alcohol, polyvinylpyrrolidone, 4-(1,1,3,3-tetramethylbutyl)-phenol polymer with ethylene oxide and formaldehyde, poloxamers, poloxamines, a charged phospholipid, dioctylsulfosuccinate (DOSS), T-1508, dialkylesters of sodium sulfosuccinic acid, sodium lauryl sulfate, alkyl aryl polyether sulfonate, a mixture of sucrose stearate and sucrose distearate, p-isononylphenoxypoly-(glycidol), Crodestas SL-40[®], C₁₈H₃₇CH₂(CON(CH₃)-CH₂(CHOH)₄(CH₂OH)₂, decanoyl-N-methylglucamide, n-decyl β-D-glucopyranoside, n-decyl β-D-maltopyranoside, n-dodecyl β-D-glucopyranoside, n-dodecyl β-D-maltoside, heptanoyl-N-methylglucamide, n-heptyl-β-D-glucopyranoside, n-heptyl β-D-thioglucoside, n-hexyl β-D-glucopyranoside, nonanoyl-N-methylglucamide, n-nonyl β-D-glucopyranoside, octanoyl-N-methylglucamide, n-octyl-β-D-glucopyranoside, octyl β-D-thioglucopyranoside

65. (New) A method for making a propellant-based dry powder composition comprising nanoparticulate drug particles and at least one propellant, wherein:

- (a) the drug particles are poorly soluble and are in crystalline form, amorphous form, or a combination thereof;
- (b) the drug particles have an effective average particle size of less than about 1000 nm, and
- (c) the drug particles have at least one surface modifier adsorbed on the surface thereof;

wherein the method comprises milling at ambient pressure or under high pressure a dispersion comprising the poorly soluble drug, at least one surface modifier and a non-aqueous liquid propellant to obtain a nanoparticulate drug composition having an effective average particle size of less than about 1000 nm, followed by obtaining dry powder of a nanoparticulate drug composition.

66. (New) The method of claim 65, wherein the propellant is selected from the group consisting of a chlorinated propellant, a non-chlorinated propellant, a hydrofluorinated alkane, and a halogenated hydrocarbon propellant having a low boiling point.

67. (New) The method of claim 65, wherein the dispersion further comprises a diluent.

68. (New) The method of claim 67, wherein essentially every diluent particle comprises at least one embedded nanoparticulate drug particle having a surface modifier adhered to the surface of the drug particle.

69. (New) The method of claim 65, wherein the drug is selected from the group consisting of proteins, peptides, elastase inhibitors, analgesics, cystic-fibrosis therapies, asthma therapies, emphysema therapies, respiratory distress syndrome therapies, chronic bronchitis therapies, chronic obstructive pulmonary disease therapies, organ-transplant rejection therapies, therapies for tuberculosis and other infections of the lung, fungal infection therapies, and respiratory illness therapies associated with acquired immune deficiency syndrome, an oncology drug, an anti-emetic, a cardiovascular agent, beclomethasone dipropionate, naproxen, triamcinolone acetonide, budesonide, and an anti-emetic.

70. (New) The method of claim 65, wherein the surface modifier is selected from the group consisting of a nonionic surfactant and an ionic surfactant.

71. (New) The method of claim 65, wherein the surface modifier is selected from the group consisting of tyloxapol, cetyl pyridinium chloride, gelatin, casein, lecithin, dextran, glycerol, gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glycerol monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers, polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters; polyethylene glycols, dodecyl trimethyl ammonium bromide, polyoxyethylene stearates, colloidal silicon dioxide, phosphates, sodium dodecylsulfate, carboxymethylcellulose calcium, hydroxypropyl cellulose, hydroxypropyl methylcellulose, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethyl-cellulose phthalate, noncrystalline cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol, polyvinylpyrrolidone, 4-(1,1,3,3-tetramethylbutyl)-phenol polymer with ethylene oxide and formaldehyde, poloxamers, poloxamines, a charged phospholipid, dioctylsulfosuccinate (DOSS), T-1508, dialkylesters of sodium sulfosuccinic acid, sodium lauryl sulfate, alkyl aryl polyether sulfonate, a mixture of sucrose stearate and sucrose distearate, p-isononylphenoxypoly-(glycidol), Crodestas SL-40[®], C₁₈H₃₇CH₂(CON(CH₃)-CH₂(CHOH)₄(CH₂OH)₂, decanoyl-N-methylglucamide, n-decyl β-D-glucopyranoside, n-decyl β-D-maltopyranoside, n-dodecyl β-D-glucopyranoside, n-dodecyl β-D-maltoside, heptanoyl-N-

methylglucamide, n-heptyl- β -D-glucopyranoside, n-heptyl β -D-thioglucoside, n-hexyl β -D-glucopyranoside, nonanoyl-N-methylglucamide, n-nonyl β -D-glucopyranoside, octanoyl-N-methylglucamide, n-octyl- β -D-glucopyranoside, octyl β -D-thioglucopyranoside

72. (New) A method for making a propellant-based dry powder composition, comprising:

- (a) obtaining dry powder of a nanoparticulate drug composition; and
- (b) dispersing the dry powder in at least one propellant,

wherein the nanoparticulate drug composition: (i) comprises a poorly soluble drug, (ii) has an effective average particle size of less than about 1000 nm, and (iii) has a surface modifier adsorbed on the surface of the drug particles.

73. (New) The method of claim 72, wherein step (a) comprises:

- (i) forming an aqueous nanoparticulate dispersion of the drug and surface modifier;
- and

(ii) spray-drying the nanoparticulate dispersion to form a dry powder of spherically shaped aggregates of the nanoparticulate drug and surface modifier, wherein the aggregates have a diameter of less than or equal to about 100 microns.

74. (New) The method of claim 73, further comprising adding a diluent to the nanoparticulate dispersion prior to spray-drying.

75. (New) The method of claim 72, wherein step (a) comprises:

- (a) forming an aqueous nanoparticulate dispersion of the drug and surface modifier;
- and

(b) freeze-drying the nanoparticulate dispersion to form a dry powder of spherically shaped aggregates of the nanoparticulate drug and surface modifier, wherein the aggregates have a diameter of less than or equal to about 100 microns.

76. (New) The method of claim 74, further comprising adding a diluent to the nanoparticulate dispersion prior to freeze-drying.

77. (New) The method of claim 72, wherein the propellant is selected from the group consisting of a chlorinated propellant, a non-chlorinated propellant, a hydrofluorinated alkane, and a halogenated hydrocarbon propellant having a low boiling point.

78. (New) The method of claim 72, wherein the drug is selected from the group consisting of proteins, peptides, elastase inhibitors, analgesics, cystic-fibrosis therapies, asthma therapies, emphysema therapies, respiratory distress syndrome therapies, chronic bronchitis therapies, chronic obstructive pulmonary disease therapies, organ-transplant rejection therapies, therapies for tuberculosis and other infections of the lung, fungal infection therapies, and respiratory illness therapies associated with acquired immune deficiency syndrome, an oncology drug, an anti-emetic, a cardiovascular agent, beclomethasone dipropionate, naproxen, triamcinolone acetonide, budesonide, and an anti-emetic.

79. (New) The method of claim 72, wherein the surface modifier is selected from the group consisting of a nonionic surfactant and an ionic surfactant.

80. (New) The method of claim 72, wherein the surface modifier is selected from the group consisting of tyloxapol, cetyl pyridinium chloride, gelatin, casein, lecithin, dextran, glycerol, gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glycerol monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers, polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters; polyethylene glycols, dodecyl trimethyl ammonium bromide, polyoxyethylene stearates, colloidal silicon dioxide, phosphates, sodium dodecylsulfate, carboxymethylcellulose calcium, hydroxypropyl cellulose, hydroxypropyl methylcellulose, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethyl-cellulose phthalate, noncrystalline cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol, polyvinylpyrrolidone, 4-(1,1,3,3-tetramethylbutyl)-phenol polymer with ethylene oxide and formaldehyde, poloxamers, poloxamines, a charged phospholipid, dioctylsulfosuccinate (DOSS), T-1508, dialkylesters of sodium sulfosuccinic acid, sodium lauryl sulfate, alkyl aryl polyether sulfonate, a mixture of sucrose stearate and sucrose distearate, p-isononylphenoxypoly-(glycidol), Crodestas SL-40[®], C₁₈H₃₇CH₂(CON(CH₃)-CH₂(CHOH)₄(CH₂OH)₂, decanoyl-N-methylglucamide, n-decyl β-D-glucopyranoside, n-decyl β-D-maltopyranoside, n-dodecyl β-D-glucopyranoside, n-dodecyl β-D-maltoside, heptanoyl-N-

methylglucamide, n-heptyl- β -D-glucopyranoside, n-heptyl β -D-thioglucoside, n-hexyl β -D-glucopyranoside, nonanoyl-N-methylglucamide, n-nonyl β -D-glucopyranoside, octanoyl-N-methylglucamide, n-octyl- β -D-glucopyranoside, octyl β -D-thioglucopyranoside

What is claimed is:

1. A nanoparticulate composition comprising:
 - (a) beclomethasone dipropionate particles having an average particle size of less than about 1000 nm; and
 - (b) at least one surface modifier.
2. The composition of claim 1, wherein the effective average particle size of the beclomethasone dipropionate particles is less than about 1000 nm, meaning that at least 90% of the particles have a particle size of less than about 1000 nm.
3. The composition of claim 1, wherein the effective average particle size of the beclomethasone dipropionate particles is less than about 400 nm, meaning that at least 90% of the particles have a particle size of less than about 400 nm.
4. The composition of claim 1, wherein the effective average particle size of the beclomethasone dipropionate particles is less than about 300 nm, meaning that at least 90% of the particles have a particle size of less than about 300 nm.
5. The composition of claim 1, wherein the effective average particle size of the beclomethasone dipropionate particles is less than about 100 nm, meaning that at least 90% of the particles have a particle size of less than about 100 nm.
6. The composition of any of claims 2-5, wherein at least 95% of the beclomethasone dipropionate particles have a particle size less than the effective average.
7. The composition of any of claims 2-5, wherein at least 99% of the beclomethasone dipropionate particles have a particle size less than the effective average.

8. The composition of claim 1, wherein the surface modifier is present in an amount of from about 0.1% to about 90%, by weight, based on the total combined weight of the beclomethasone dipropionate and surface modifier.

9. The composition of claim 1, wherein the surface modifier is present in an amount of from about 0.1% to about 75%, by weight, based on the total combined weight of the beclomethasone dipropionate and surface modifier.

10. The composition of claim 1, wherein the surface modifier is present in an amount of from about 20% to about 60%, by weight, based on the total combined weight of the beclomethasone dipropionate and surface modifier.

11. The composition of claim 1, formulated as an aqueous dispersion.

12. The composition of claim 1, formulated as a dispersion in a liquid media selected from the group consisting of aqueous salt solutions, safflower oil, and a solvent.

13. The composition of claim 12, wherein the solvent is selected from the group consisting of ethanol, t-butanol, hexane, and glycol.

14. The composition of claim 1, formulated as a dry composition.

15. The composition of claim 1, comprising two or more surface modifiers.

16. The composition of claim 1, wherein the surface modifier is selected from the group consisting of nonionic and ionic surfactants.

17. The composition of claim 1, wherein the surface modifier is selected from the group consisting of gelatin, casein, lecithin, gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glycerol monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers, polyoxyethylene castor oil derivatives, polyoxyethylene

sorbitan fatty acid esters, polyethylene glycols, polyoxyethylene stearates, colloidal silicon dioxide, phosphates, sodium dodecylsulfate, carboxymethylcellulose calcium, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose phthalate, noncrystalline cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol, polyvinylpyrrolidone, tyloxapol, poloxamers, poloxamines, dextran, dialkylesters of sodium sulfosuccinic acid, sodium lauryl sulfate, alkyl aryl polyether sulfonate, mixtures of sucrose stearate and sucrose distearate, $C_{18}H_{37}CH_2C(O)N(CH_3)-CH_2(CHOH)_4(CH_2OH)_2$, decanoyl-N-methylglucamide, n-decyl- β -D-glucopyranoside, n-decyl- β -D-maltopyranoside, n-dodecyl- β -D-glucopyranoside, n-dodecyl- β -D-maltoside, heptanoyl-N-methylglucamide, n-heptyl- β -D-glucopyranoside, n-heptyl- β -D-thioglucoside, n-hexyl- β -D-glucopyranoside, nonanoyl-N-methylglucamide, n-nonyl- β -D-glucopyranoside, octanoyl-N-methylglucamide, n-octyl- β -D-glucopyranoside, octyl- β -D-thioglucopyranoside, p-isononylphenoxypoly(glycidol), dioctylsulfosuccinate (DOSS), glycerol, dodecyl trimethyl ammonium bromide, a charged phospholipid, the triblock copolymer B20-3800, and the triblock copolymer B20-5000.

18. The composition of claim 17, wherein the surface modifier is selected from the group consisting of block copolymers of ethylene oxide and propylene oxide, tetrafunctional block copolymer derived from sequential addition of propylene oxide and ethylene oxide to ethylenediamine, a dioctyl ester of sodium sulfosuccinic acid, and dimyristoyl phosphatidyl glycerol.

19. The composition of claim 1, wherein the surface modifier is polyvinyl alcohol.

20. A method of making a nanoparticulate beclomethasone dipropionate composition comprising contacting particles of beclomethasone dipropionate with at least one surface stabilizer for a time and under conditions to reduce the average particle size of the beclomethasone dipropionate particles to less than about 1000 nm.

21. The method of claim 20, comprising:

- (a) dispersing particles of beclomethasone dipropionate in a liquid dispersion media in which the particles are poorly soluble; and
- (b) applying mechanical means in the presence of grinding media to reduce the average particle size of beclomethasone dipropionate to less than about 1000 nm,

wherein the beclomethasone dipropionate particles are reduced in size in the presence of at least one surface modifier, or wherein at least one surface modifier is added to the liquid dispersion media following particle size reduction of beclomethasone dipropionate.

22. The method of claim 21, wherein the mechanical means is a dispersion mill.

23. The method of claim 22, wherein the dispersion mill is selected from the group consisting of a ball mill, an attritor mill, a vibratory mill, and a media mill.

24. The method of claim 20 or 21, wherein the time required to reduce the particle size of beclomethasone dipropionate is from about 1 minute up to about 5 days.

25. The method of claim 20 or 21, wherein the beclomethasone dipropionate particles are reduced in size at an ambient temperature.

26. The method of claim 20 or 21, wherein the beclomethasone dipropionate particles are reduced in size at a less than about of less than about 40°C.

27. The method of claim 21, wherein the grinding media is spherical in shape and has an average particle size of from about 0.1 mm to about 3 mm.

28. The method of claim 27, wherein the grinding media has an average particle size of from 0.2 mm to about 2 mm.

29. The method of claim 28, wherein the grinding media has an average particle size of from 0.25 mm to about 1 mm.

30. The method of claim 28, wherein the grinding media has an average particle size of from 0.25 mm to about 1 mm.

31. The method of claim 21, wherein the grinding media is spherical in shape and has an average particle size of less than about 75 microns.

32. The method of claim 21, wherein the grinding media has a density greater than about 3 g/cm³.

33. The method of claim 21, wherein the grinding media comprises a compound selected from the group consisting of zirconium oxide, zirconium silicate, glass, stainless steel, titania, alumina, 95% ZrO₂ stabilized with yttrium, and polymeric resin grinding media.

34. The method of claim 33, wherein the grinding media comprises spherical particles consisting essentially of a polymeric resin.

35. The method of claim 33, wherein the grinding media comprises spherical particles comprising a core which is coated with a polymeric resin.

36. The method of claim 33, wherein the polymeric resin is selected from the group consisting of crosslinked polystyrenes, styrene copolymers, polycarbonates, polyacetals, vinyl chloride polymers, vinyl chloride copolymers, polyurethanes, polyamides, fluoropolymers, high density polyethylenes, polypropylenes, cellulose ethers, cellulose esters, polyhydroxymethacrylate, polyhydroxyethyl acrylate, and silicone containing polymers.

37. The method of claim 36, wherein the polymeric resin is selected from the group consisting of polystyrene crosslinked with divinylbenzene, poly(tetrafluoroethylenes), cellulose acetate, and polysiloxanes.

38. The method of claim 33, wherein the polymeric resin is biodegradable.

39. The method of claim 37, wherein the biodegradable polymer is selected from the group consisting of poly(lactides), poly(glycolide) copolymers of lactides, copolymers of glycolide, polyanhydrides, poly(hydroxyethyl methacrylate), poly(imino carbonates), poly(N-acylhydroxyproline)esters, poly(N-palmitoyl hydroxyproline) esters, ethylene-vinyl acetate copolymers, poly(orthoesters), poly(caprolactones), and poly(phosphazenes).

40. The method of claim 33, wherein the polymeric resin has a density of from about 0.8 to about 3.0 g/cm³.

41. The method of claim 35, wherein the core material of the grinding media is selected from the group consisting of zirconium oxides, zirconium silicate, glass, stainless steel, titania, alumina, and ferrite.

42. The method of claim 35, wherein the core material of the grinding media has a density greater than about 2.5 g/cm³.

43. The method of claim 35, wherein the thickness of the polymeric resin coating on the core is from about 1 to about 500 microns.

44. The method of claim 35, wherein the thickness of the polymeric resin coating on the core is less than the diameter of the core.

45. The method of claim 21, comprising:

(a) continuously introducing particles of beclomethasone dipropionate and rigid grinding media into a milling chamber,

(b) contacting the beclomethasone dipropionate particles with the grinding media while in the chamber to reduce the particle size of the beclomethasone dipropionate particles;

(c) continuously removing beclomethasone dipropionate particles and the grinding media from the milling chamber, and

(d) separating the beclomethasone dipropionate particles from the grinding media.

46. The method of claim 21, comprising recirculating the beclomethasone dipropionate particles and the grinding media through the milling chamber.

47. The method of claim 21, comprising using grinding media having more than one particle size.

48. The method of claim 47, comprising at least two sizes of grinding media:

- (a) having a mean particle size between about 1 and 300 μm ; and
- (b) having a mean particle size between about 300 and 1000 μm .

49. The method of claim 20, wherein the effective average particle size of the beclomethasone dipropionate particles is selected from the group consisting of less than about 1000 μm , less than about 400 μm , less than about 300 μm , and less than about 100 μm , meaning that at least 90% of the particles have a particle size less than the effective average.

50. The method of claim 49, wherein at least 95% of the beclomethasone dipropionate particles have a particle size less than the effective average.

51. The method of claim 49, wherein at least 99% of the beclomethasone dipropionate particles have a particle size less than the effective average.

52. The method of claim 20, wherein the surface modifier is present in an amount selected from the group consisting of from about 0.1% to about 90%, about 0.1% to about 75%, and about 20% to about 60%, by weight, based on the total combined weight of the beclomethasone dipropionate and surface modifier.

53. The method of claim 20, utilizing two or more surface modifiers.

54. The method of claim 20, wherein the surface modifier is selected from the group consisting of nonionic and ionic surfactants.

55. The method of claim 20, wherein the surface modifier is selected from the group consisting of gelatin, casein, lecithin, gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glycerol monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers, polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters, polyethylene glycols, polyoxyethylene stearates, colloidal silicon dioxide, phosphates, sodium dodecylsulfate, carboxymethylcellulose calcium, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hydroxy propylcellulose, hydroxypropylmethylcellulose phthalate, noncrystalline cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol, polyvinylpyrrolidone, tyloxapol, poloxamers, poloxamines, dextran, dialkylesters of sodium sulfosuccinic acid, sodium lauryl sulfate, alkyl aryl polyether sulfonate, mixtures of sucrose stearate and sucrose distearate, $C_{18}H_{37}CH_2C(O)N(CH_3)-CH_2(CHOH)_4(CH_2OH)_2$, decanoyl-N-methylglucamide, n-decyl- β -D-glucopyranoside, n-decyl- β -D-maltopyranoside, n-dodecyl- β -D-glucopyranoside, n-dodecyl- β -D-maltoside, heptanoyl-N-methylglucamide, n-heptyl- β -D-glucopyranoside, n-heptyl- β -D-thioglucoside, n-hexyl- β -D-glucopyranoside, nonanoyl-N-methylglucamide, n-nonyl- β -D-glucopyranoside, octanoyl-N-methylglucamide, n-octyl- β -D-glucopyranoside, octyl- β -D-thioglucopyranoside, p-isononylphenoxypoly(glycidol), dioctylsulfosuccinate (DOSS), glycerol, dodecyl trimethyl ammonium bromide, a charged phospholipid, the triblock copolymer B20-3800, and the triblock copolymer B20-5000.

56. The method of claim 55, wherein the surface modifier is selected from the group consisting of block copolymers of ethylene oxide and propylene oxide, tetrafunctional block copolymer derived from sequential addition of propylene oxide and ethylene oxide to ethylenediamine, a dioctyl ester of sodium sulfosuccinic acid, and dimyristoyl phosphatidyl glycerol.

57. The method of claim 20, wherein the surface modifier is polyvinyl alcohol.

58. A method of making a nanoparticulate beclomethasone dipropionate composition comprising

- (a) dissolving beclomethasone dipropionate in an aqueous base with stirring;
- (b) adding the solution of beclomethasone dipropionate with stirring to a solution of one or more surface modifiers to form a clear solution;
- (c) neutralizing the formulation from step (b) with stirring with an appropriate acid solution, and
- (d) recovering particles of beclomethasone dipropionate having an average particle size of less than about 1000 nm.

59. The method of claim 58, further comprising removing any formed salt by dialysis or diafiltration.

60. The method of claim 58, further comprising concentrating the resulting beclomethasone dipropionate dispersion to a desired concentration of beclomethasone dipropionate.

61. The method of claim 58, wherein step (c) is carried out in semicontinuous, continuous batch, or continuous methods at constant flow rates of the reacting components.

62. The method of claim 58, further comprising dissolving a crystal growth modifier in step (a) with the beclomethasone dipropionate.

63. The method of claim 58, wherein the effective average particle size of the beclomethasone dipropionate particles is selected from the group consisting of less than about 1000 nm, less than about 400 nm, less than about 300 nm, and less than about 100 nm, meaning that at least 90% of the particles have a particle size less than the effective average.

64. The method of claim 63, wherein at least 95% of the beclomethasone dipropionate particles have a particle size less than the effective average.

65. The method of claim 63, wherein at least 99% of the beclomethasone dipropionate particles have a particle size less than the effective average.

Amendments to the Claims:

This listing of claims will replace all prior versions, and listings, of claims in the application.

Listing of Claims:

1-86. (Cancelled)

87. (New) An angiogenesis inhibitor composition consisting of:
- (a) particles of an angiogenesis inhibitor, wherein the angiogenesis inhibitor is paclitaxel or a salt thereof, having an effective average particle size of less than about 2000 nm; and
 - (b) associated with the surface thereof at least one surface stabilizer, wherein the surface stabilizer is essentially free of intermolecular cross linkages.
88. (New) The composition of claim 87, wherein the angiogenesis inhibitor is selected from the group consisting of a crystalline phase, an amorphous phase, and a semi-crystalline phase,.
89. (New) The composition of claim 87, wherein the effective average particle size of the angiogenesis inhibitor is selected from the group consisting of less than about 1900 nm, less than about 1800 nm, less than about 1700 nm, less than about 1600 nm, less than about 1500 nm, less than about 1400 nm, less than about 1300 nm, less than about 1200 nm, less than about 1100 nm, less than about 1000 nm, less than about 900 nm, less than about 800 nm, less than about 700 nm, less than about 600 nm, less than about 500 nm, less than about 400 nm, less than about 300 nm, less than about 250 nm, less than about 200 nm, less than about 100 nm, less than about 75 nm, and less than about 50 nm.
90. (New) The composition of claim 87, wherein the composition is formulated for administration selected from the group consisting of oral, pulmonary, rectal, ophthalmic, colonic, parenteral, intracisternal, intravaginal, intraperitoneal, local, buccal, nasal, and topical administration.

91. (New) The composition of claim 87, wherein the composition is formulated into a dosage form selected from the group consisting of liquid dispersions, gels, aerosols, ointments, creams, controlled release formulations, fast melt formulations, lyophilized formulations, tablets, capsules, delayed release formulations, extended release formulations, pulsatile release formulations, and mixed immediate release and controlled release formulations.
92. (New) An angiogenesis inhibitor composition consisting of:
- (a) particles of an angiogenesis inhibitor, wherein the angiogenesis inhibitor is paclitaxel or a salt thereof, having an effective average particle size of less than about 2000 nm;
 - (b) associated with the surface thereof at least one surface stabilizer, wherein the surface stabilizer is essentially free of intermolecular cross linkages; and
 - (c) one or more pharmaceutically acceptable excipients, carriers, or a combination thereof.
93. (New) The composition of claim 87, wherein the angiogenesis inhibitor is present in an amount selected from the group consisting of from about 99.5% to about 0.001%, from about 95% to about 0.1%, and from about 90% to about 0.5%, by weight, based on the total combined weight of the angiogenesis inhibitor and at least one surface stabilizer, not including other excipients.
94. (New) The composition of claim 87, wherein the at least one surface stabilizer is present in an amount selected from the group consisting of from about 0.5% to about 99.999%, from about 5.0% to about 99.9%, and from about 10% to about 99.5%, by weight, based on the total combined weight of the at least one angiogenesis inhibitor and at least one surface stabilizer, not including other excipients.
95. (New) The composition of claim 87, comprising at least two surface stabilizers.

96. (New) The composition of claim 87, wherein the surface stabilizer is selected from the group consisting of a non-ionic surface stabilizer, an anionic surface stabilizer, a cationic surface stabilizer, an ionic surface stabilizer, and a zwitterionic surface stabilizer.

97. (New) The composition of claim 96, wherein at least one surface stabilizer is selected from the group consisting of hexyldecyl trimethyl ammonium chloride (CTAC), albumin, bovine serum albumin, human serum albumin, cetyl pyridinium chloride, gelatin, casein, phosphatides, dextran, glycerol, gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glycerol monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers, polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters, polyethylene glycols, dodecyl trimethyl ammonium bromide, polyoxyethylene stearates, colloidal silicon dioxide, phosphates, sodium dodecylsulfate, carboxymethylcellulose calcium, hydroxypropyl celluloses, hydroxypropyl methylcellulose, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hydroxypropylmethyl-cellulose phthalate, noncrystalline cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol, polyvinylpyrrolidone, 4-(1,1,3,3-tetramethylbutyl)-phenol polymer with ethylene oxide and formaldehyde, poloxamers; poloxamines, a charged phospholipid, dioctylsulfosuccinate, dialkylesters of sodium sulfosuccinic acid, sodium lauryl sulfate, alkyl aryl polyether sulfonates, mixtures of sucrose stearate and sucrose distearate, $C_{18}H_{37}CH_2C(O)N(CH_3)-CH_2(CHOH)_4(CH_2OH)_2$, p-isononylphenoxypoly-(glycidol), decanoyl-N-methylglucamide; n-decyl β -D-glucopyranoside; n-decyl β -D-maltopyranoside; n-dodecyl β -D-glucopyranoside; n-dodecyl β -D-maltoside; heptanoyl-N-methylglucamide; n-heptyl- β -D-glucopyranoside; n-heptyl β -D-thioglucoside; n-hexyl β -D-glucopyranoside; nonanoyl-N-methylglucamide; n-nonyl β -D-glucopyranoside; octanoyl-N-methylglucamide; n-octyl- β -D-glucopyranoside; octyl β -D-thioglucopyranoside; lysozyme, PEG-phospholipid, PEG-cholesterol, PEG-cholesterol derivative, PEG-vitamin A, PEG-vitamin E, and random copolymers of vinyl acetate and vinyl pyrrolidone.

98. (New) The composition of claim 87, wherein upon administration the composition redisperses such that the angiogenesis inhibitor particles have a particle size selected from the

group consisting of less than about 2 microns, less than about 1900 nm, less than about 1800 nm, less than about 1700 nm, less than about 1600 nm, less than about 1500 nm, less than about 1400 nm, less than about 1300 nm, less than about 1200 nm, less than about 1100 nm, less than about 1000 nm, less than about 900 nm, less than about 800 nm, less than about 700 nm, less than about 600 nm, less than about 500 nm, less than about 400 nm, less than about 300 nm, less than about 250 nm, less than about 200 nm, less than about 150 nm, less than about 100 nm, less than about 75 nm, and less than about 50 nm.

99. (New) The composition of claim 87, wherein the composition does not produce significantly different absorption levels when administered under fed as compared to fasting conditions.

100. (New) The composition of claim 87, wherein the difference in absorption of the angiogenesis inhibitor composition of the invention, when administered in the fed versus the fasted state, is selected from the group consisting of less than about 100%, less than about 90%, less than about 80%, less than about 70%, less than about 60%, less than about 50%, less than about 40%, less than about 35%, less than about 30%, less than about 25%, less than about 20%, less than about 15%, less than about 10%, less than about 5%, and less than about 3%.

101. (New) The composition of claim 87, wherein the composition does not produce significantly different rates of absorption (T_{\max}) when administered under fed as compared to fasting conditions.

102. (New) The composition of claim 87, wherein the difference in the T_{\max} for the angiogenesis inhibitor composition of the invention, when administered in the fed versus the fasted state, is less than about 100%, less than about 90%, less than about 80%, less than about 70%, less than about 60%, less than about 50%, less than about 40%, less than about 30%, less than about 20%, less than about 15%, less than about 10%, less than about 5%, and less than about 3%.

103. (New) The composition of claim 87, wherein upon administration the T_{\max} is less than that of a conventional non-nanoparticulate composition of the same angiogenesis inhibitor, administered at the same dosage.

104. (New) The composition of claim 87, wherein in comparative pharmacokinetic testing with a non-nanoparticulate composition of the same angiogenesis inhibitor, administered at the same dosage, the composition exhibits a T_{\max} selected from the group consisting of less than about 100%, less than about 90%, less than about 80%, less than about 70%, less than about 60%, less than about 50%, less than about 40%, less than about 30%, less than about 25%, less than about 20%, less than about 15%, and less than about 10% of the T_{\max} exhibited by the non-nanoparticulate composition of the angiogenesis inhibitor.

105. (New) The composition of claim 87, wherein following administration the composition has a T_{\max} selected from the group consisting of less than about 2.5 hours, less than about 2.25 hours, less than about 2 hours, less than about 1.75 hours, less than about 1.5 hours, less than about 1.25 hours, less than about 1.0 hours, less than about 50 minutes, less than about 40 minutes, less than about 30 minutes, less than about 25 minutes, less than about 20 minutes, less than about 15 minutes, and less than about 10 minutes.

106. (New) The composition of claim 87, wherein upon administration the C_{\max} of the composition is greater than the C_{\max} of a conventional non-nanoparticulate composition of the same angiogenesis inhibitor, administered at the same dosage.

107. (New) The composition of claim 87, wherein in comparative pharmacokinetic testing with a non-nanoparticulate composition of the same angiogenesis inhibitor, administered at the same dosage, the nanoparticulate composition exhibits a C_{\max} selected from the group consisting of greater than about 5%, greater than about 10%, greater than about 15%, greater than about 20%, greater than about 30%, greater than about 40%, greater than about 50%, greater than about 60%, greater than about 70%, greater than about 80%, greater than about 90%, greater than about 100%, greater than about 110%, greater than about 120%, greater than about 130%, greater than about 140%, and greater than about 150% than the C_{\max} exhibited by the non-nanoparticulate composition of the angiogenesis inhibitor.

108. (New) A method of making a solvent-free angiogenesis inhibitor composition comprising contacting particles of at least one angiogenesis inhibitor, wherein the angiogenesis inhibitor is paclitaxel or a salt thereof, with at least one surface stabilizer, wherein the surface stabilizer is essentially free of intermolecular cross linkages, for a time and under conditions sufficient to provide an angiogenesis inhibitor composition having an effective average particle size of less than about 2 microns.
109. (New) The method of claim 108, wherein said contacting comprises grinding.
110. (New) The method of claim 109, wherein said grinding comprises wet grinding.
111. (New) The method of claim 108, wherein said contacting comprises homogenizing.
112. (New) The method of claim 108, wherein said contacting comprises:
- (a) dissolving the angiogenesis inhibitor particles in a solvent;
 - (b) adding the resulting angiogenesis inhibitor solution to a solution comprising at least one surface stabilizer; and
 - (c) precipitating the solubilized angiogenesis inhibitor having at least one surface stabilizer associated with the surface thereof by the addition thereto of a non-solvent.
113. (New) The method of claim 108, wherein the angiogenesis inhibitor is selected from the group consisting of a crystalline phase, an amorphous phase, and a semi-crystalline phase.
114. (New) The method of claim 108, wherein the effective average particle size of the nanoparticulate angiogenesis inhibitor particles is selected from the group consisting of less than about 1900 nm, less than about 1800 nm, less than about 1700 nm, less than about 1600 nm, less than about 1500 nm, less than about 1400 nm, less than about 1300 nm, less than about 1200 nm, less than about 1100 nm, less than about 1000 nm, less than about 900 nm, less than about 800 nm, less than about 700 nm, less than about 600 nm, less than about 500 nm, less than about 400 nm, less than about 300 nm, less than about 250 nm, less than about 200 nm, less than about 100 nm, less than about 75 nm, and less than about 50 nm.

115. (New) The method of claim 108, wherein the angiogenesis inhibitor is present in an amount selected from the group consisting of from about 99% to about 0.001%, from about 95% to about 0.5%, and from about 90% to about 0.5%, by weight, based on the total combined weight of the angiogenesis inhibitor and at least one surface stabilizer, not including other excipients.

116. (New) The method of claim 108, wherein at least one surface stabilizer is present in an amount selected from the group consisting of from about 0.5% to about 99.999%, from about 5.0% to about 99.9%, and from about 10% to about 99.5%, by weight, based on the total combined dry weight of the angiogenesis inhibitor and at least one surface stabilizer, not including other excipients.

117. (New) The method of claim 108, wherein the angiogenesis inhibitor particles are contacted with at least two surface stabilizers.

118. (New) The method of claim 108, wherein the surface stabilizer is selected from the group consisting of a non-ionic surface stabilizer, an anionic surface stabilizer, a cationic surface stabilizer, an ionic surface stabilizer, and a zwitterionic surface stabilizer.

119. (New) The method of claim 118, wherein at least one surface stabilizer is selected from the group consisting of hexyldecyl trimethyl ammonium chloride (CTAC), albumin, bovine serum albumin, human serum albumin, cetyl pyridinium chloride, gelatin, casein, phosphatides, dextran, glycerol, gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glycerol monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers, polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters, polyethylene glycols, dodecyl trimethyl ammonium bromide, polyoxyethylene stearates, colloidal silicon dioxide, phosphates, sodium dodecylsulfate, carboxymethylcellulose calcium, hydroxypropyl celluloses, hydroxypropyl methylcellulose, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hydroxypropylmethyl-cellulose phthalate, noncrystalline cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol, polyvinylpyrrolidone, 4-(1,1,3,3-tetramethylbutyl)-phenol polymer with ethylene oxide and formaldehyde,

poloxamers; poloxamines, a charged phospholipid, dioctylsulfosuccinate, dialkylesters of sodium sulfosuccinic acid, sodium lauryl sulfate, alkyl aryl polyether sulfonates, mixtures of sucrose stearate and sucrose distearate, $C_{18}H_{37}CH_2C(O)N(CH_3)-CH_2(CHOH)_4(CH_2OH)_2$, p-isononylphenoxypoly-(glycidol), decanoyl-N-methylglucamide; n-decyl β -D-glucopyranoside; n-decyl β -D-maltopyranoside; n-dodecyl β -D-glucopyranoside; n-dodecyl β -D-maltoside; heptanoyl-N-methylglucamide; n-heptyl- β -D-glucopyranoside; n-heptyl β -D-thioglucoside; n-hexyl β -D-glucopyranoside; nonanoyl-N-methylglucamide; n-nonyl β -D-glucopyranoside; octanoyl-N-methylglucamide; n-octyl- β -D-glucopyranoside; octyl β -D-thioglucopyranoside; lysozyme, PEG-phospholipid, PEG-cholesterol, PEG-cholesterol derivative, PEG-vitamin A, PEG-vitamin E, and random copolymers of vinyl acetate and vinyl pyrrolidone.

120. (New) A method of treating a subject in need with an angiogenesis inhibitor composition comprising administering to the subject an effective amount of a solvent-free angiogenesis inhibitor composition consisting of:

- (a) particles of an angiogenesis inhibitor, wherein the angiogenesis inhibitor is paclitaxel or a salt thereof, having an effective average particle size of less than about 2000 nm; and
- (b) associated with the surface thereof at least one surface stabilizer, wherein the surface stabilizer is essentially free of intermolecular cross linkages.

121. (New) The method of claim 120, wherein the angiogenesis inhibitor is selected from the group consisting of a crystalline phase, an amorphous phase, and a semi-crystalline phase.

122. (New) The method of claim 120, wherein the effective average particle size of the nanoparticulate angiogenesis inhibitor particles is selected from the group consisting of less than about 1900 nm, less than about 1800 nm, less than about 1700 nm, less than about 1600 nm, less than about 1500 nm, less than about 1400 nm, less than about 1300 nm, less than about 1200 nm, less than about 1100 nm, less than about 1000 nm, less than about 900 nm, less than about 800 nm, less than about 700 nm, less than about 600 nm, less than about 500

nm, less than about 400 nm, less than about 300 nm, less than about 250 nm, less than about 200 nm, less than about 100 nm, less than about 75 nm, and less than about 50 nm.

123. (New) The method of claim 120, wherein the composition is formulated for an administration form selected from the group consisting of oral, pulmonary, rectal, ophthalmic, colonic, parenteral, intracisternal, intravaginal, intraperitoneal, local, buccal, nasal, and topical administration.

124. (New) The method of claim 120, wherein the composition is in a dosage form selected from the group consisting of liquid dispersions, gels, aerosols, ointments, creams, controlled release formulations, fast melt formulations, lyophilized formulations, tablets, capsules, delayed release formulations, extended release formulations, pulsatile release formulations, and mixed immediate release and controlled release formulations.

125. (New) The method of claim 120, wherein the composition further comprises one or more pharmaceutically acceptable excipients, carriers, or a combination thereof.

126. (New) The method of claim 120, wherein the angiogenesis inhibitor is present in an amount selected from the group consisting of from about 99% to about 0.001%, from about 95% to about 0.5%, and from about 90% to about 0.5%, by weight, based on the total combined weight of the angiogenesis inhibitor and at least one surface stabilizer, not including other excipients.

127. (New) The method of claim 120, wherein at least one surface stabilizer is present in an amount selected from the group consisting of from about 0.5% to about 99.999%, from about 5.0% to about 99.9%, and from about 10% to about 99.5%, by weight, based on the total combined dry weight of angiogenesis inhibitor and at least one surface stabilizer, not including other excipients.

128. (New) The method of claim 120, wherein the angiogenesis inhibitor composition comprises at least two surface stabilizers.

129. (New) The method of claim 120, wherein the surface stabilizer is selected from the group consisting of a non-ionic surface stabilizer, an anionic surface stabilizer, a cationic surface stabilizer, an ionic surface stabilizer, and a zwitterionic surface stabilizer.

130. (New) The method of claim 129, wherein the at least one surface stabilizer is selected from the group consisting of hexyldecyl trimethyl ammonium chloride (CTAC), albumin, bovine serum albumin, human serum albumin, cetyl pyridinium chloride, gelatin, casein, phosphatides, dextran, glycerol, gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glycerol monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers, polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters, polyethylene glycols, dodecyl trimethyl ammonium bromide, polyoxyethylene stearates, colloidal silicon dioxide, phosphates, sodium dodecylsulfate, carboxymethylcellulose calcium, hydroxypropyl celluloses, hydroxypropyl methylcellulose, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hydroxypropylmethyl-cellulose phthalate, noncrystalline cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol, polyvinylpyrrolidone, 4-(1,1,3,3-tetramethylbutyl)-phenol polymer with ethylene oxide and formaldehyde, poloxamers; poloxamines, a charged phospholipid, dioctylsulfosuccinate, dialkylesters of sodium sulfosuccinic acid, sodium lauryl sulfate, alkyl aryl polyether sulfonates, mixtures of sucrose stearate and sucrose distearate, $C_{18}H_{37}CH_2C(O)N(CH_3)-CH_2(CHOH)_4(CH_2OH)_2$, p-isononylphenoxypoly-(glycidol), decanoyl-N-methylglucamide; n-decyl β -D-glucopyranoside; n-decyl β -D-maltopyranoside; n-dodecyl β -D-glucopyranoside; n-dodecyl β -D-maltoside; heptanoyl-N-methylglucamide; n-heptyl- β -D-glucopyranoside; n-heptyl β -D-thioglucoside; n-hexyl β -D-glucopyranoside; nonanoyl-N-methylglucamide; n-nonyl β -D-glucopyranoside; octanoyl-N-methylglucamide; n-octyl- β -D-glucopyranoside; octyl β -D-thioglucopyranoside; lysozyme, PEG-phospholipid, PEG-cholesterol, PEG-cholesterol derivative, PEG-vitamin A, PEG-vitamin E, and random copolymers of vinyl acetate and vinyl pyrrolidone.

131. (New) The method of claim 120, wherein the composition does not produce significantly different absorption levels when administered under fed as compared to fasting conditions.

132. (New) The method of claim 120, wherein the difference in absorption of the nanoparticulate angiogenesis inhibitor composition of the invention, when administered in the fed versus the fasted state, is selected from the group consisting of less than about 100%, less than about 90%, less than about 80%, less than about 70%, less than about 60%, less than about 50%, less than about 40%, less than about 35%, less than about 30%, less than about 25%, less than about 20%, less than about 15%, less than about 10%, less than about 5%, and less than about 3%.

133. (New) The method of claim 120, wherein the composition does not produce significantly different rates of absorption (T_{\max}) when administered under fed as compared to fasting conditions.

134. (New) The method of claim 120, wherein the difference in the T_{\max} for the nanoparticulate angiogenesis inhibitor composition of the invention, when administered in the fed versus the fasted state, is less than about 100%, less than about 90%, less than about 80%, less than about 70%, less than about 60%, less than about 50%, less than about 40%, less than about 30%, less than about 20%, less than about 15%, less than about 10%, less than about 5%, and less than about 3%.

135. (New) The method of claim 120, wherein upon administration the T_{\max} is less than that of a conventional non-nanoparticulate composition of the same angiogenesis inhibitor, administered at the same dosage.

136. (New) The method of claim 120, wherein the nanoparticulate angiogenesis inhibitor composition exhibits a T_{\max} , as compared to a non-nanoparticulate composition of the same angiogenesis inhibitor administered at the same dosage, selected from the group consisting of less than about 90%, less than about 80%, less than about 70%, less than about 60%, less than about 50%, less than about 40%, less than about 30%, less than about 25%, less than about

20%, less than about 15%, and less than about 10% of the T_{\max} exhibited by the non-nanoparticulate composition of the angiogenesis inhibitor.

137. (New) The method of claim 120, wherein upon administration the T_{\max} of the composition is selected from the group consisting of less than about 2.5 hours, less than about 2.25 hours, less than about 2 hours, less than about 1.75 hours, less than about 1.5 hours, less than about 1.25 hours, less than about 1.0 hours, less than about 50 minutes, less than about 40 minutes, less than about 30 minutes, less than about 25 minutes, less than about 20 minutes, less than about 15 minutes, and less than about 10 minutes.

138. (New) The method of claim 120, wherein upon administration the C_{\max} of the composition is greater than the C_{\max} of a conventional non-nanoparticulate composition of the same angiogenesis inhibitor, administered at the same dosage.

139. (New) The method of claim 120, wherein the nanoparticulate angiogenesis inhibitor composition exhibits a C_{\max} , as compared to a non-nanoparticulate composition of the same angiogenesis inhibitor administered at the same dosage, selected from the group consisting of greater than about 5%, greater than about 10%, greater than about 15%, greater than about 20%, greater than about 30%, greater than about 40%, greater than about 50%, greater than about 60%, greater than about 70%, greater than about 80%, greater than about 90%, greater than about 100%, greater than about 110%, greater than about 120%, greater than about 130%, greater than about 140%, and greater than about 150% than the C_{\max} exhibited by the non-nanoparticulate composition of the angiogenesis inhibitor.

140. (New) The method of claim 120, wherein the method is used to treat an condition where a selective angiogenesis inhibitor is indicated.

141. (New) The method of claim 120, wherein the method is used to treat a mammalian disease characterized by undesirable angiogenesis.

142. (New) The method of claim 120, wherein the method is used to treat or prevent tumor growth.

143. (New) The method of claim 120, wherein the method is used to treat or prevent cancer growth.
144. (New) The method of claim 120, wherein the subject is a human.
145. (New) The composition of claim 87, wherein:
- (a) the angiogenesis inhibitor is paclitaxel; and
 - (b) the surface stabilizer is not Tween 20, polyvinyl alcohol, hexyldecyl trimethyl ammonium chloride (CTAC), Aerosol OT, poloxamer 188 (also known as Pluronic F68), Tetronic 908, or Tween 80.
146. (New) The method of claim 108, wherein:
- (a) the angiogenesis inhibitor is paclitaxel; and
 - (b) the surface stabilizer is not Tween 20, polyvinyl alcohol, hexyldecyl trimethyl ammonium chloride (CTAC), Aerosol OT, poloxamer 188 (also known as Pluronic F68), Tetronic 908, or Tween 80.
147. (New) The method of claim 120, wherein:
- (a) the angiogenesis inhibitor is paclitaxel; and
 - (b) the surface stabilizer is not Tween 20, polyvinyl alcohol, hexyldecyl trimethyl ammonium chloride (CTAC), Aerosol OT, poloxamer 188 (also known as Pluronic F68), Tetronic 908, or Tween 80.
148. (New) A neoplastic inhibitor composition comprising:
- (a) particles of a neoplastic inhibitor or a salt thereof having an effective average particle size of less than about 2000 nm; and
 - (b) associated with the surface thereof at least one non-crosslinked surface stabilizer.

WHAT IS CLAIMED IS:

1. A sterile composition comprising:
 - (a) particles comprising at least one active agent selected from the group consisting of docetaxel, salts of docetaxel, derivatives of docetaxel, conjugates of docetaxel and analogues of docetaxel, wherein the particles have an effective average particle size of less than about 2000 nm; and
 - (b) at least one surface stabilizer adsorbed on a surface of the particles, wherein the composition is sterilized by exposure to gamma radiation.
2. The composition of claim 1, wherein the active agent is in a form selected from the group consisting of crystalline, amorphous, semi-crystalline, semi-amorphous, and mixtures thereof.
3. The composition of claim 1, wherein the active agent is docetaxel.
4. The composition of claim 3, wherein the docetaxel is in a form selected from the group consisting of an anhydrous, a hydrated, and a trihydrate crystal form, and mixtures thereof.
5. The composition of claim 1, wherein the effective average particle size is selected from the group consisting of less than: about 1900 nm, about 1800 nm, about 1700 nm, about 1600 nm, about 1500 nm, about 1400 nm, about 1300 nm, about 1200 nm, about 1100 nm, about 1000 nm, about 900 nm, about 800 nm, about 700 nm, about 650 nm, about 600 nm, about 550 nm, about 500 nm, about 450 nm, about 400 nm, about 350 nm, about 300 nm, about 250 nm, about 200 nm, about 150 nm, about 100 nm, about 75 nm, and about 50 nm.
6. The composition of claim 1, wherein the composition is formulated:
 - (a) for routes of administration selected from the group consisting of oral, pulmonary, rectal, ophthalmic, colonic, parenteral, intracisternal, intravaginal, intraperitoneal, local, buccal, nasal, and topical administration;

(b) into a dosage form selected from the group consisting of liquid dispersions, solid dispersions, liquid-filled capsules, gels, aerosols, ointments, creams, lyophilized formulations, tablets, capsules, multi-particulate filled capsules, tablets composed of multi-particulates, compressed tablets, and capsules filled with enteric-coated beads of the active agent;

(c) into a dosage form selected from the group consisting of controlled release formulations, fast melt formulations, delayed release formulations, extended release formulations, pulsatile release formulations, and mixed immediate release and controlled release formulations; or

(d) any combination of (a), (b), and (c).

7. The composition of claim 6, wherein the composition is an injectable formulation.

8. The composition of claim 6, wherein the composition is formulated for pulmonary administration.

9. The composition of claim 6, wherein the composition is in a solid form.

10. The composition of claim 6, wherein the composition is in a liquid form.

11. The composition of claim 1, wherein:

(a) the at least one surface stabilizer is present in an amount selected from the group consisting of about 1%, 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95% or 99%, by weight, based on the total combined dry weight of the active agent and the at least one surface stabilizer, not including other excipients;

(b) the particles are present in an amount selected from the group consisting of about 1%, 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95% or 99%, by weight, based on the total combined weight of the particles comprising the active agent and the at least one surface stabilizer, not including other excipients; or

(c) a combination of (a) and (b).

12. The composition of claim 1, wherein the at least one surface stabilizer is selected from the group consisting of an anionic surface stabilizer, a cationic surface

stabilizer, a zwitterionic surface stabilizer, a non-ionic surface stabilizer, and an ionic surface stabilizer.

13. The composition of claim 1, wherein the at least one surface stabilizer is selected from the group consisting of povidone, cetyl pyridinium chloride, albumin, human serum albumin, bovine serum albumin, gelatin, casein, phosphatides, dextran, glycerol, gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glycerol monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers, polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters, polyethylene glycols, dodecyl trimethyl ammonium bromide, polyoxyethylene stearates, colloidal silicon dioxide, phosphates, sodium dodecylsulfate, carboxymethylcellulose calcium, hydroxypropyl celluloses, hypromellose, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hypromellose phthalate, noncrystalline cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol, polyvinylpyrrolidone, 4-(1,1,3,3-tetramethylbutyl)-phenol polymer with ethylene oxide and formaldehyde, poloxamers; poloxamines, a charged phospholipid, dioctylsulfosuccinate, dialkylesters of sodium sulfosuccinic acid, sodium lauryl sulfate, sodium deoxycholate, alkyl aryl polyether sulfonates, mixtures of sucrose stearate and sucrose distearate, p-isononylphenoxypoly-(glycidol), decanoyl-N-methylglucamide; n-decyl b-D-glucopyranoside; n-decyl b-D-maltopyranoside; n-dodecyl b-D-glucopyranoside; n-dodecyl b-D-maltoside; heptanoyl-N-methylglucamide; n-heptyl-b-D-glucopyranoside; n-heptyl b-D-thioglucoside; n-hexyl b-D-glucopyranoside; nonanoyl-N-methylglucamide; n-nonyl b-D-glucopyranoside; octanoyl-N-methylglucamide; n-octyl-b-D-glucopyranoside; octyl b-D-thioglucopyranoside; lysozyme, PEG-phospholipid, PEG-cholesterol, PEG-cholesterol derivative, PEG-vitamin A, PEG-vitamin E, random copolymers of vinyl acetate and vinyl pyrrolidone, a cationic polymer, a cationic biopolymer, a cationic polysaccharide, a cationic cellulosic, a cationic alginate, a cationic nonpolymeric compound, a cationic phospholipids, cationic lipids, polymethylmethacrylate trimethylammonium bromide, sulfonium compounds, polyvinylpyrrolidone-2-dimethylaminoethyl methacrylate dimethyl sulfate, hexadecyltrimethyl ammonium bromide, phosphonium compounds, quaternary ammonium compounds, benzyl-di(2-chloroethyl)ethylammonium bromide, coconut trimethyl ammonium chloride, coconut trimethyl ammonium bromide, coconut methyl dihydroxyethyl ammonium chloride, coconut methyl dihydroxyethyl ammonium bromide, decyl triethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride bromide, C₁₂₋₁₅dimethyl hydroxyethyl ammonium chloride, C₁₂-

₁₅dimethyl hydroxyethyl ammonium chloride bromide, coconut dimethyl hydroxyethyl ammonium chloride, coconut dimethyl hydroxyethyl ammonium bromide, myristyl trimethyl ammonium methyl sulphate, lauryl dimethyl benzyl ammonium chloride, lauryl dimethyl benzyl ammonium bromide, lauryl dimethyl (ethenoxy)₄ ammonium chloride, lauryl dimethyl (ethenoxy)₄ ammonium bromide, N-alkyl (C₁₂₋₁₈)dimethylbenzyl ammonium chloride, N-alkyl (C₁₄₋₁₈)dimethyl-benzyl ammonium chloride, N-tetradecyldimethylbenzyl ammonium chloride monohydrate, dimethyl didecyl ammonium chloride, N-alkyl and (C₁₂₋₁₄) dimethyl 1-naphthylmethyl ammonium chloride, trimethylammonium halide, alkyl-trimethylammonium salts, dialkyl-dimethylammonium salts, lauryl trimethyl ammonium chloride, ethoxylated alkyamidoalkyldialkylammonium salt, an ethoxylated trialkyl ammonium salt, dialkylbenzene dialkylammonium chloride, N-didecyldimethyl ammonium chloride, N-tetradecyldimethylbenzyl ammonium, chloride monohydrate, N-alkyl(C₁₂₋₁₄) dimethyl 1-naphthylmethyl ammonium chloride, dodecyldimethylbenzyl ammonium chloride, dialkyl benzenealkyl ammonium chloride, lauryl trimethyl ammonium chloride, alkylbenzyl methyl ammonium chloride, alkyl benzyl dimethyl ammonium bromide, C₁₂ trimethyl ammonium bromides, C₁₅ trimethyl ammonium bromides, C₁₇ trimethyl ammonium bromides, dodecylbenzyl triethyl ammonium chloride, poly-diallyldimethylammonium chloride (DADMAC), dimethyl ammonium chlorides, alkyldimethylammonium halogenides, tricetyl methyl ammonium chloride, decyltrimethylammonium bromide, dodecyltriethylammonium bromide, tetradecyltrimethylammonium bromide, methyl trioctylammonium chloride, POLYQUAT 10™, tetrabutylammonium bromide, benzyl trimethylammonium bromide, choline esters, benzalkonium chloride, stearylalkonium chloride compounds, cetyl pyridinium bromide, cetyl pyridinium chloride, halide salts of quaternized polyoxyethylalkylamines, MIRAPOL™, ALKAQUAT™, alkyl pyridinium salts; amines, amine salts, amine oxides, imide azolinium salts, protonated quaternary acrylamides, methylated quaternary polymers, and cationic guar.

14. The composition of claim 13, wherein the at least one surface stabilizer is povidone.

15. The composition of claim 13, wherein the at least one surface stabilizer is sodium deoxycholate.

16. The composition of claim 1, wherein the at least one surface stabilizer is selected from the group consisting of poloxamer 188, poloxamer 338, poloxamer 407, polysorbate 80, and lecithin.
17. The composition of claim 1 further comprising at least one excipient.
18. The composition of claim 1, wherein the at least one surface stabilizer is a protein.
19. The composition of claim 18, wherein the surface stabilizer is an albumin.
20. The composition of claim 19, wherein the albumin is human serum albumin.
21. The composition of claim 17 wherein the at least one excipient is a sugar selected from the group consisting of sucrose, mannitol, dextrose, lactose, sorbitol, maltose, and trehalose.
22. The composition of claim 17, wherein the at least one excipient is selected from the group consisting of a bulking agent, a crystal growth inhibitor, a free radical scavenger agent, and a redispersion agent.
23. The composition of claim 17, wherein the at least one excipient is present in the amount selected from the group consisting of from about 5 to about 95, about 10 to about 95, about 20 to about 95, about 50 to about 90, about 60 to about 90, about 70 to about 90, or about 70 to about 80, measured by % w/w of the dry composition.
24. The composition of claim 1, wherein the gamma radiation provides a total dose of radiation selected from the group consisting of from about 5 to about 50 kGray, about 15 kGray to about 40 kGray, about 15 to about 30 kGray, and about 20 to about 30 kGray.
25. The composition of claim 1, wherein the gamma radiation provides a total dose of about 25 kGray.
26. A dry composition comprising about 18.87% docetaxel, about 4.72% povidone, about 0.94% sodium deoxycholate, about 56.60% sucrose, and about 18.87% mannitol.

27. A dry composition comprising about 18.87% docetaxel, about 4.72% povidone, about 0.94% sodium deoxycholate, about 37.74% sucrose, and about 37.74% mannitol.

28. The composition of claim 1, wherein the active agent is selected from the group consisting of:

- (a) docetaxel analogues comprising cyclohexyl groups instead of phenyl groups at the C-3' benzoate position, the C-2 benzoate positions, or a combination thereof;
- (b) docetaxel analogues lacking phenyl or an aromatic group at C-3' or C-2 position;
- (c) 2-amido docetaxel analogues;
- (d) docetaxel analogues lacking the oxetane D-ring but possessing the 4 α -acetoxy group;
- (e) 5(20)deoxydocetaxel;
- (f) 10-deoxy-10-C-morpholinoethyl docetaxel analogues;
- (g) analogues having a t-butyl carbamate as the isoserine N-acyl substituent, but differing from docetaxel at C-10 (acetyl group versus hydroxyl) and at the C-13 isoserine linkage (enol ester versus ester);
- (h) docetaxel analogues having a peptide side chain at C3;
- (i) XRP9881 (10-deacetyl baccatin III docetaxel analogue);
- (j) XRP6528 (10-deacetyl baccatin III docetaxel analogue);
- (k) Ortataxel (14-beta-hydroxy-deacetyl baccatin III docetaxel analogue);
- (l) MAC-321 (10-deacetyl-7-propanoyl baccatin docetaxel analogue);
- (m) DJ-927 (7-deoxy-9-beta-dihydro-9,10, O-acetal taxane docetaxal analogue);
- (n) docetaxel analogues having C2-C3'N-linkages bearing an aromatic ring at position C2, and tethered between N3' and the C2-aromatic ring at the ortho position;

(o) docetaxel analogues having C2-C3'N-linkages bearing an aromatic ring at position C2, and tethered between N3' and the C2-aromatic ring at the meta position;

(p) docetaxel analogues bearing 22-membered (or more) rings connecting the C-2 OH and C-3' NH moieties;

(q) 7beta-O-glycosylated docetaxel analogues;

(r) 10-alkylated docetaxel analogues;

(s) 2',2'-difluoro docetaxel analogues;

(t) 3'-(2-furyl) docetaxel analogues;

(u) 3'-(2-pyrrolyl) docetaxel analogues; and

(v) fluorescent and biotinylated docetaxel analogues.

29. The composition of claim 28, wherein the docetaxel analogue is selected from the group consisting of:

(a) 3'-dephenyl-3'-cyclohexyldocetaxel;

(b) 2-(hexahydro)docetaxel;

(c) 3'-dephenyl-3'-cyclohexyl-2-(hexahydro)docetaxel;

(d) 3'-dephenyl-3'-cyclohexyldocetaxel;

(e) 2-(hexahydro)docetaxel;

(f) m-methoxy docetaxel analogues;

(g) m-chlorobenzoylamido docetaxel analogues;

(h) 5(20)-thia docetaxel analogues;

(i) docetaxel analogues in which the 7-hydroxyl group is modified to the hydrophobic group methoxy;

(j) docetaxel analogues in which the 7-hydroxyl group is modified to the hydrophobic group deoxy;

(k) docetaxel analogues in which the 7-hydroxyl group is modified to the hydrophobic group 6,7-olefin;

(l) docetaxel analogues in which the 7-hydroxyl group is modified to the hydrophobic group alpha-F;

(m) docetaxel analogues in which the 7-hydroxyl group is modified to the hydrophobic group 7-beta-8-beta-methano;

(n) docetaxel analogues in which the 7-hydroxyl group is modified to the hydrophobic group fluoromethoxy;

(o) 10-alkylated docetaxel analogue having a methoxycarbonyl group at the end of the alkyl moiety;

(p) docetaxel analogues that possess a N-(7-nitrobenz-2-oxa-1,3-diazo-4-yl)amido-6-caproyl chain in position 7 or 3';

(q) docetaxel analogues that possess a N-(7-nitrobenz-2-oxa-1,3-diazo-4-yl)amido-3-propanoyl group at 3'; and

(r) docetaxel analogues that possess a 5'-biotinyl amido-6-caproyl chain in position 7, 10 or 3'.

30. A method for making a sterilized nanoparticulate composition comprising the steps of:

lyophilizing an aqueous dispersion comprising at least one active agent selected from the group consisting of docetaxel, salts of docetaxel, derivatives of docetaxel, conjugates of docetaxel and analogues of docetaxel, wherein the particles have an effective average particle size of less than about 2000 nm, and at least one surface stabilizer adsorbed on a surface of the particles, to form a lyo; and

sterilizing the lyo to produce a sterilized composition.

31. The method of claim 30, further comprising before the lyophilizing step, the step of mixing the at least one active agent selected from the group consisting of docetaxel, salts of docetaxel, derivatives of docetaxel, conjugates of docetaxel and analogues of docetaxel, and the at least one surface stabilizer in an aqueous medium for a period of time and under conditions sufficient to provide the aqueous dispersion.

32. The method of claim 31, wherein the mixing step is selected from the group consisting of milling, attrition, homogenizing, precipitating, supercritical fluids processing, freezing, nano-electrospraying techniques, or any combination thereof.

33. The method of claim 30, wherein the sterilizing step comprises exposing the lyo to a gamma radiation dose selected from the group consisting of from about 5 to about 50 kGray, about 15 kGray to about 40 kGray, about 15 to about 30 kGray, and about 20 to about 30 kGray..

34. The method of claim 30, wherein the sterilizing step comprises exposing the lyo to about 25 kGray of gamma radiation.

35. The method of claim 30, wherein the aqueous dispersion further comprises at least one excipient selected from the group consisting of a bulking agent, a crystal growth inhibitor, a free radical scavenger agent, and a redispersion agent.

36. The method of claim 30, wherein the aqueous dispersion before the lyophilizing step has an effective average particle size selected from the group consisting of less than about 2000 nm, less than about 1900 nm, less than about 1800 nm, less than about 1700 nm, less than about 1600 nm, less than about 1500 nm, less than about 1400 nm, less than about 1300 nm, less than about 1200 nm, less than about 1100 nm, less than about 1 micron, less than about 900 nm, less than about 800 nm, less than about 700 nm, less than about 600 nm, less than about 500 nm, less than about 400 nm, less than about 300 nm, less than about 250 nm, less than about 200 nm, less than about 150 nm, less than about 100 nm, less than about 75 nm, and less than about 50 nm.

37. The method of claim 30 further comprising, after the sterilizing step, the step of redispersing the lyo in an aqueous medium forming a post-sterilized dispersion having an effective average particle size selected from the group consisting of less than about 2

microns, less than about 1900 nm, less than about 1800 nm, less than about 1700 nm, less than about 1600 nm, less than about 1500 nm, less than about 1400 nm, less than about 1300 nm, less than about 1200 nm, less than about 1100 nm, less than about 1 micron, less than about 900 nm, less than about 800 nm, less than about 700 nm, less than about 600 nm, less than about 500 nm, less than about 400 nm, less than about 300 nm, less than about 250 nm, less than about 200 nm, less than about 150 nm, less than about 100 nm, less than about 75 nm, and less than about 50 nm.

39. A terminally sterilized lyophilization composition made from the steps comprising:

milling at least one active agent selected from the group consisting of docetaxel, salts of docetaxel, derivatives of docetaxel, conjugates of docetaxel and analogues of docetaxel, an excipient selected from the group consisting of a bulking agent, a crystal growth inhibitor, a free radical scavenger agent, a redispersion agent, and at least one surface stabilizer, with milling media in an aqueous medium for a period of time and under conditions sufficient to provide a dispersion of particles of the at least one active agent having an effective average particle size of less than about 2000 nm, and the at least one surface stabilizer adsorbed on the surface of the particles;

removing the milling media from the dispersion;

lyophilizing the dispersion to form a lyo; and

sterilizing the lyo to produce a sterilized composition.

40. The composition of claim 39, wherein the sterilizing step comprises exposing the lyo to a dose of gamma radiation effective to produce sterilization.

41. A method of treating a subject in need of docetaxel or a salt, derivative, conjugate or analogue thereof comprising administering to the subject an effective amount of a composition comprising:

(a) particles comprising docetaxel, a salt, derivative, conjugate or analogue thereof, wherein the particles have an effective average particle size of less than about 2000 nm; and

(b) at least one surface stabilizer adsorbed on a surface of the particles,
wherein the composition is sterilized by exposure to gamma radiation.

42. The method of claim 41, wherein the composition is administered by injection.

43. A sterile liquid dosage form of docetaxel for intravenous administration comprising:

(a) about 5% by weight particles of at least one active agent selected from the group consisting of docetaxel, salts of docetaxel, derivatives of docetaxel, conjugates of docetaxel and analogues of docetaxel, the particles having an effective average particle size of less than about 2000 nm;

(b) two surface stabilizers, one or both of the surface stabilizers is adsorbed on a surface of particles;

(c) sucrose; and

(d) mannitol,

wherein the composition is sterilized by exposure to gamma radiation, and wherein the composition is administered to a patient at a dosage amount selected from the group consisting of about 100, 200, 300, 400, 500, 600, 700, 800, 900 and 1000 mg/m².

AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions of claims in the application.

Claims 1 – 9 (Cancelled).

10. (New) A pharmaceutical composition of an immunosuppressive agent comprising solid particles of the agent coated with one or more surface modifiers, wherein the particles have an average effective particle size of less than about 50 nm to less than about 1000 nm.

11. (New) The composition of claim 10, wherein the surface modifier is selected from the group consisting of: anionic surfactants, cationic surfactants, zwitterionic surfactants, nonionic surfactants, surface active biological modifiers, and combinations thereof.

12. (New) The composition of claim 11, wherein the surface modifier is selected from the group consisting of: alkyl sulfonates, alkyl phosphates, triethanolamine stearate, sodium lauryl sulfate, sodium dodecylsulfate, alkyl polyoxyethylene sulfates, sodium alginate, dioctyl sodium sulfosuccinate, sodium carboxymethylcellulose, calcium carboxymethylcellulose, benzalkonium chloride, phosphatidylglycerol, polyoxyethylene fatty alcohol ethers, polyoxyethylene sorbitan fatty acid esters, polyoxyethylene fatty acid esters, sorbitan esters, glycerol monostearate, polyethylene glycols, polypropylene glycols, cetyl alcohol, cetostearyl alcohol, polyoxyethylene-polyoxypropylene copolymers, polaxamines, methylcellulose, hydroxy propylcellulose, hydroxy propylmethylcellulose and noncrystalline cellulose.

13. (New) The composition of claim 11, wherein the surface modifier is a phospholipid.

14. (New) The composition of claim 11, wherein the surface active biological modifier is a protein.
15. (New) The composition of claim 13, wherein the protein is casein.
16. (New) The composition of claim 10, wherein the surface modifier comprises a copolymer of oxyethylene and oxypropylene.
17. (New) The composition of claim 16, wherein the copolymer of oxyethylene and oxypropylene is a block copolymer.
18. (New) The composition of claim 11, further comprising a pH adjusting agent.
19. (New) The composition of claim 10, wherein the immunosuppressive agent is beclomethasone.

AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions of claims in the application.

1. (Previously Presented) A stable nanoparticulate α -integrin antagonist composition comprising:
 - (a) particles of at least one α -integrin antagonist or a salt thereof having an effective average particle size of less than 2000 nm; and
 - (b) at least one surface stabilizer selected from the group consisting of copolymers of vinyl pyrrolidone, copolymers of vinyl acetate, and a combination thereof.
2. (Original) The composition of claim 1, wherein the nanoparticulate α -integrin antagonist is an $\alpha_4\beta_1$ -integrin antagonist.
3. (Original) The composition of claim 2, wherein the $\alpha_4\beta_1$ -integrin antagonist is ELND001.
4. (Previously Presented) The α -integrin antagonist of claim 1, wherein the α -integrin antagonist is in a crystalline phase, a semi-crystalline phase, an amorphous phase and mixtures thereof.
5. (Previously Presented) The composition of claim 1, wherein the effective average particle size of the nanoparticulate α -integrin antagonist particles is selected from the group consisting of less than 1900 nm, less than 1800 nm, less than 1700 nm, less than 1600 nm, less than 1500 nm, less than 1400 nm, less than 1300 nm, less than 1200 nm, less than 1100 nm, less than 1000 nm, less than 900 nm, less than 800 nm, less than 700 nm, less than 650 nm, less than 600 nm, less than 550 nm, less than 500 nm, less than 450 nm, less than 400 nm, less than 350 nm, less than 300 nm, less than 250 nm, less than 200 nm, less than 150 nm, less than 100 nm, less than 75 nm, or less than 50 nm.

6. (Currently Amended) The composition of claim 1, wherein the composition is formulated:

~~——(a)——~~ for administration selected from the group consisting of oral, pulmonary, intravenous, rectal, ophthalmic, colonic, parenteral, intracisternal, intravaginal, intraperitoneal, local, buccal, nasal, and topical administration;

~~——(b)——~~ into a dosage form selected from the group consisting of liquid dispersions, gels, aerosols, ointments, creams, tablets, and capsules;

~~——(c)——~~ into a dosage form selected from the group consisting of lyophilized formulations, fast melt formulations, controlled release formulations, delayed release formulations, extended release formulations, pulsatile release formulations, and mixed immediate release and controlled release formulations; or

~~——(d)——~~ any combination of (a), (b), and (c).

7. (Original) The composition of claim 1, wherein the composition further comprises one or more pharmaceutically acceptable excipients, carriers, or a combination thereof.

8. (Previously Presented) The composition of claim 1 wherein:

(a) the amount of the α -integrin antagonist is selected from the group consisting of from 99.5% to 0.001%, from 95% to 0.1%, and from 90% to 0.5%, by weight, based on the total combined weight of the α -integrin antagonist and at least one surface stabilizer, not including other excipients;

(b) at least one surface stabilizer is present in an amount selected from the group consisting of from 0.01% to 99.5% by weight, from 0.1% to 95% by weight, and from 0.5% to 90% by weight, based on the total combined dry weight of the α -integrin antagonist and the at least one surface stabilizer, not including other excipients; or

(c) a combination of (a) and (b).

9. (Previously Presented) The composition of claim 1, wherein the surface stabilizer is copolymers of vinyl pyrrolidone.

10. (Previously Presented) The composition of claim 1, wherein at least one surface stabilizer is copolymers of vinyl acetate.

11. (Previously Presented) The composition claim 1, wherein:

(a) upon administration to a mammal the α -integrin antagonist particles redisperse such that the particles have an effective average particle size selected from the group consisting of less than 2 microns, less than 1900 nm, less than 1800 nm, less than 1700 nm, less than 1600 nm, less than 1500 nm, less than 1400 nm, less than 1300 nm, less than 1200 nm, less than 1100 nm, less than 1000 nm, less than 900 nm, less than 800 nm, less than 700 nm, less than 600 nm, less than 500 nm, less than 400 nm, less than 300 nm, less than 250 nm, less than 200 nm, less than 150 nm, less than 100 nm, less than 75 nm, and less than 50 nm;

(b) the composition redisperses in a biorelevant media such that the α -integrin antagonist particles have an effective average particle size selected from the group consisting of less than 2 microns, less than 1900 nm, less than 1800 nm, less than 1700 nm, less than 1600 nm, less than 1500 nm, less than 1400 nm, less than 1300 nm, less than 1200 nm, less than 1100 nm, less than 1000 nm, less than 900 nm, less than 800 nm, less than 700 nm, less than 600 nm, less than 500 nm, less than 400 nm, less than 300 nm, less than 250 nm, less than 200 nm, less than 150 nm, less than 100 nm, less than 75 nm, and less than 50 nm; or

(c) a combination of (a) and (b).

12. (Original) The composition of claim 11, wherein the biorelevant media is selected from the group consisting of water, aqueous electrolyte solutions, aqueous solutions of a salt, aqueous solutions of an acid, aqueous solutions of a base, and combinations thereof.

13. (Original) The composition of claim 1, wherein:

(a) the T_{\max} of the α -integrin antagonist, when assayed in the plasma of a mammalian subject following administration, is less than the T_{\max} for a non-nanoparticulate composition of

the same α -integrin antagonist, administered at the same dosage;

(b) the C_{\max} of the α -integrin antagonist, when assayed in the plasma of a mammalian subject following administration, is greater than the C_{\max} for a non-nanoparticulate composition of the same α -integrin antagonist, administered at the same dosage;

(c) the AUC of the α -integrin antagonist, when assayed in the plasma of a mammalian subject following administration, is greater than the AUC for a non-nanoparticulate composition of the same α -integrin antagonist, administered at the same dosage; or

(d) any combination of (a), (b), and (c).

14. (Previously Presented) The composition of claim 13, wherein:

(a) the T_{\max} is selected from the group consisting of not greater than 90%, not greater than 80%, not greater than 70%, not greater than 60%, not greater than 50%, not greater than 30%, not greater than 25%, not greater than 20%, not greater than 15%, not greater than 10%, and not greater than 5% of the T_{\max} exhibited by a non-nanoparticulate composition of the same α -integrin antagonist, administered at the same dosage;

(b) the C_{\max} is selected from the group consisting of at least 50%, at least 100%, at least 200%, at least 300%, at least 400%, at least 500%, at least 600%, at least 700%, at least 800%, at least 900%, at least 1000%, at least 1100%, at least 1200%, at least 1300%, at least 1400%, at least 1500%, at least 1600%, at least 1700%, at least 1800%, or at least 1900% greater than the C_{\max} exhibited by a non-nanoparticulate composition of the same α -integrin antagonist, administered at the same dosage;

(c) the AUC is selected from the group consisting of at least 25%, at least 50%, at least 75%, at least 100%, at least 125%, at least 150%, at least 175%, at least 200%, at least 225%, at least 250%, at least 275%, at least 300%, at least 350%, at least 400%, at least 450%, at least 500%, at least 550%, at least 600%, at least 750%, at least 700%, at least 750%, at least 800%, at least 850%, at least 900%, at least 950%, at least 1000%, at least 1050%, at least 1100%, at least 1150%, or at least 1200% greater than the AUC exhibited by the non-

nanoparticulate formulation of the same α -integrin antagonist, administered at the same dosage;
or

- (d) any combination of (a), (b), and (c).

15. (Previously Presented) The composition of claim 1, wherein the C_{\max} of the α -integrin antagonist, when assayed in the plasma of the mammalian subject, is selected from the group consisting of greater than 1 $\mu\text{g/mL}$, greater than 3 $\mu\text{g/mL}$, greater than 5 $\mu\text{g/mL}$, greater than 10 $\mu\text{g/mL}$, and greater than 15 $\mu\text{g/mL}$.

- 16. (Cancelled)

17. (Previously Presented) The composition of claim 16, wherein the difference in absorption of the active agent composition of the invention, when administered in the fed versus the fasted state, is selected from the group consisting of less than 100%, less than 90%, less than 80%, less than 70%, less than 60%, less than 50%, less than 40%, less than 30%, less than 25%, less than 20%, less than 15%, less than 10%, less than 5%, and less than 3%.

18. (Original) The composition of claim 1, wherein administration of the composition to a human in a fasted state is bioequivalent to administration of the composition to a subject in a fed state.

19. (Original) The composition of claim 18, wherein "bioequivalency" is established by:

- (a) a 90% Confidence Interval of between 0.80 and 1.25 for both C_{\max} and AUC; or
- (b) a 90% Confidence Interval of between 0.80 and 1.25 for AUC and a 90%

Confidence Interval of between 0.70 to 1.43 for C_{\max} .

20. (Previously Presented) The composition of claim 1, additionally comprising a α -integrin antagonist composition having an effective average particle size which is greater than 2 microns.

21. (Previously Presented) The composition of claim 1, additionally comprising at least one additional nanoparticulate α -integrin antagonist composition, having an effective average particle size of less than 2 microns, wherein the additional nanoparticulate α -integrin antagonist composition has an effective average particle size which is different than particle size of the nanoparticulate α -integrin antagonist composition of claim 1.

22. (Original) The composition of claim 1, additionally comprising at least one non- α -integrin antagonist active agent selected from the group consisting of proteins, peptides, nucleotides, anti-obesity drugs, nutraceuticals, dietary supplements, carotenoids, corticosteroids, elastase inhibitors, anti-fungals, alkylxanthine, oncology therapies, anti-emetics, analgesics, opioids, antipyretics, cardiovascular agents, anti-inflammatory agents, anthelmintics, anti-arrhythmic agents, antibiotics, anticoagulants, antidepressants, antidiabetic agents, antiepileptics, antihistamines, antihypertensive agents, antimuscarinic agents, antimycobacterial agents, antineoplastic agents, immunosuppressants, antithyroid agents, antiviral agents, anxiolytics, sedatives, astringents, beta-adrenoceptor blocking agents, blood products, blood substitutes, cardiac inotropic agents, contrast media, corticosteroids, cough suppressants, diagnostic agents, diagnostic imaging agents, diuretics, dopaminergics, haemostatics, immunological agents, lipid regulating agents, muscle relaxants, parasympathomimetics, parathyroid calcitonin and biphosphonates, prostaglandins, radio- pharmaceuticals, sex hormones, anti-allergic agents, stimulants, anoretics, sympathomimetics, thyroid agents, Mu receptor antagonists, Kappa receptor antagonists, non-narcotic analgesics, monoamine uptake inhibitors, adenosine regulating agents, cannabinoid derivatives, Substance P antagonists, neurokinin-1 receptor antagonists, and sodium channel blockers.

23. (Original) The composition of claim 22, wherein:

(a) the nutraceutical is selected from the group consisting of lutein, folic acid, fatty acids, fruit extracts, vegetable extracts, vitamin supplements, mineral supplements, phosphatidylserine, lipoic acid, melatonin, glucosamine/chondroitin, Aloe Vera, Guggul, glutamine, amino acids, green tea, lycopene, whole foods, food additives, herbs, phytonutrients, antioxidants, flavonoid constituents of fruits, evening primrose oil, flax seeds, fish oils, marine animal oils, and probiotics; or

(b) the anti-inflammatory agent is a COX-2 inhibitor selected from the group consisting of celecoxib, rofecoxib, valdecoxib, parecoxib, MK-966, etoricoxib, 4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide, N-(2-cyclohexyloxy-4-nitrophenyl)methane sulfonamide, methyl sulfone spiro(2.4)hept-5-ene I, SC-57666, celecoxib, SC-558, SC-560, etodolac, 5,5-dimethyl-3-(3-fluorophenyl)-4-(4-methylsulfonyl)phenyl 2(5H)-furanone, MK-476, L-745337, L-761066, L-761000, L-748780, L-748731, 5-Bromo-2-(4-fluorophenyl)-3-(4-(methylsulfonyl)phenyl, 1-(7-tert.-butyl-2,3-dihydro-3,3-dimethylbenzo(b)furan-5-yl)-4-cyclopropylbutan-1-one, 3-formylamino-7-methylsulfonylamino-6-phenoxy-4H-1-benzopyran-4-one, BF 389, PD 136005, PD 142893, PD 145065, flurbiprofen, nimesulide, nabumetone, flosulide, piroxicam, diclofenac, COX-189, D 1367, 4 nitro 2 phenoxy methane sulfonanilide, (3 benzoyldifluoromethane sulfonanilide, diflumidone), JTE-522, 4'-Acetyl-2'-(2,4-difluorophenoxy)methanesulfonanilide, FK 867, FR 115068, GR 253035, RWJ 63556, RWJ 20485, ZK 38997, (E)-(5)-(3,5-di-tert-butyl-4-hydroxybenzylidene)-2-ethyl-1,2-isothiazolidine-1,1-dioxide indomethacin, CL 1004, RS 57067, RS 104894, SC 41930, SB 205312, SKB 209670, and Ono 1078; or

(c) the non- α -integrin antagonist active agent is selected from the group consisting of aceclofenac, acemetacin, e-acetamidocaproic acid, acetaminophen, acetaminosalol, acetanilide, acetylsalicylic acid, S-adenosylmethionine, alclofenac, alfentanil, allylprodine, alminoprofen, aloxiprin, alphaprodine, aluminum bis(acetylsalicylate), amfenac, aminochlorthenoxazin, 3-amino-4-hydroxybutyric acid, 2-amino-4-picoline, aminopropylon, aminopyrine, amixetrine, ammonium salicylate, ampiroxicam, amtolmetin guacil, anileridine, antipyrine, antipyrine

salicylate, antrafenine, apazone, bendazac, benorylate, benoxaprofen, benzpiperylon, benzydamine, benzylmorphine, bermoprofen, bezitramide, bisabolol, bromfenac, p-bromoacetanilide, 5-bromosalicylic acid acetate, bromosaligenin, bucetin, bucloxic acid, bucolome, bufexamac, bumadizon, buprenorphine, butacetin, butibufen, butophanol, calcium acetylsalicylate, carbamazepine, carbiphen, carprofen, carsalam, chlorobutanol, chlorthenoxazin, choline salicylate, cinchophen, cinmetacin, ciramadol, clidanac, clometacin, clonitazene, clonixin, clopirac, clove, codeine, codeine methyl bromide, codeine phosphate, codeine sulfate, cropropamide, crotethamide, desomorphine, dexoxadrol, dextromoramide, dezocine, diampromide, diclofenac sodium, difenamizole, difenpiramide, diflunisal, dihydrocodeine, dihydrocodeinone enol acetate, dihydromorphine, dihydroxyaluminum acetylsalicylate, dimenoxadol, dimepheptanol, dimethylthiambutene, dioxaphetyl butyrate, dipipanone, diprocetyl, dipyrone, ditazol, droxicam, emorfazone, enfenamic acid, epirizole, eptazocine, etersalate, ethenzamide, ethoheptazine, ethoxazene, ethylmethylthiambutene, ethylmorphine, etodolac, etofenamate, etonitazene, eugenol, felbinac, fenbufen, fenclozic acid, fendosal, fenoprofen, fentanyl, fentiazac, fepradinol, feprazone, floctafenine, flufenamic acid, flunoxaprofen, fluoresone, flupirtine, fluproquazone, flurbiprofen, fosfosal, gentisic acid, glafenine, glucametacin, glycol salicylate, guaiazulene, hydrocodone, hydromorphone, hydroxypethidine, ibufenac, ibuprofen, ibuproxam, imidazole salicylate, indomethacin, indoprofen, isofezolac, isoladol, isomethadone, isonixin, isoxepac, isoxicam, ketobemidone, ketoprofen, ketorolac, p-lactophenetide, lefetamine, levorphanol, lofentanil, lonazolac, lomoxicam, loxoprofen, lysine acetylsalicylate, magnesium acetylsalicylate, meclofenamic acid, mefenamic acid, meperidine, meptazinol, mesalamine, metazocine, methadone hydrochloride, methotrimeprazine, metiazinic acid, metofoline, metopon, mofebutazone, mofezolac, morazone, morphine, morphine hydrochloride, morphine sulfate, morpholine salicylate, myrophine, nabumetone, nalbuphine, 1-naphthyl salicylate, naproxen, narceine, nefopam, nicomorphine, nifenazone, niflumic acid, nimesulide, 5'-nitro-2'-propoxyacetanilide, norlevorphanol, normethadone, normorphine, norpipanone, olsalazine, opium, oxaceprol, oxametacine, oxaprozin, oxycodone, oxymorphone, oxyphenbutazone, papaveretum, paranyline, parsalimide,

pentazocine, perisoxal, phenacetin, phenadoxone, phenazocine, phenazopyridine hydrochloride, phenocoll, phenoperidine, phenopyrazone, phenyl acetylsalicylate, phenylbutazone, phenyl salicylate, phenyramidol, piketoprofen, piminodine, pipebuzone, piperylone, pirofen, pirazolac, piritramide, piroxicam, pranoprofen, proglumetacin, proheptazine, promedol, propacetamol, propiram, propoxyphene, propyphenazone, proquazone, protizinic acid, ramifenazone, remifentanil, rimazolium metilsulfate, salacetamide, salicin, salicylamide, salicylamide o-acetic acid, salicylsulfuric acid, salsalte, salverine, simetride, sodium salicylate, sufentanil, sulfasalazine, sulindac, superoxide dismutase, suprofen, suxibuzone, talniflumate, tenidap, tenoxicam, terofenamate, tetrandrine, thiazolinobutazone, tiaprofenic acid, tiaramide, tilidine, tinoridine, tolfenamic acid, tolmetin, tramadol, tropesin, viminol, xenbucin, ximoprofen, zaltoprofen, and zomepirac.

24. (Previously Presented) The composition of claim 22 wherein at least one of the non- α -integrin antagonist active agents has an effective average particle size of less than 2 microns.

25. (Original) The composition of claim 22 wherein at least one of the non- $\alpha_4\beta_1$ -integrin antagonist active agents is formulated as a conventional particle size.

26. (Previously Presented) A method of making a nanoparticulate composition comprising contacting an α -integrin antagonist active agent particles with at least one surface stabilizer for a time and under conditions sufficient to provide a nanoparticulate α -integrin antagonist composition having an effective average particle size of less than 2000 nm, wherein the surface stabilizer is selected from the group consisting of copolymers of vinyl pyrrolidone, copolymers of vinyl acetate, and a combination thereof.

27. (Original) The method of claim 26, wherein the nanoparticulate α -integrin antagonist is an $\alpha_4\beta_1$ -integrin antagonist.

28. (Original) The method of claim 27, wherein the $\alpha_4\beta_1$ -integrin antagonist is ELND001.

29. (Original) The method of claim 26 wherein the contacting comprises grinding, wet grinding, homogenizing, precipitation, supercritical fluid particle generation techniques, or emulsion techniques.

30. (Previously Presented) The method of claim 26, wherein the effective average particle size of the nanoparticulate α -integrin antagonist particles is selected from the group consisting of less than 1900 nm, less than 1800 nm, less than 1700 nm, less than 1600 nm, less than 1500 nm, less than 1400 nm, less than 1300 nm, less than 1200 nm, less than 1100 nm, less than 1000 nm, less than 900 nm, less than 800 nm, less than 700 nm, less than 600 nm, less than 500 nm, less than 400 nm, less than 300 nm, less than 250 nm, less than 200 nm, less than 150 nm, less than 100 nm, less than 75 nm, and less than 50 nm.

31. (Previously Presented) A method of treating a subject in need with a nanoparticulate integrin antagonist formulation comprising administering to the subject an effective amount of a nanoparticulate composition comprising:

(a) particles of at least one α -integrin antagonist or a salt thereof having an effective average particle size of less than 2000 nm; and

(b) at least one surface stabilizer selected from the group consisting of copolymers of vinyl pyrrolidone, copolymers of vinyl acetate, and a combination thereof.

32. (Original) The method of claim 31, wherein the nanoparticulate α -integrin antagonist is an $\alpha_4\beta_1$ -integrin antagonist.

33. (Original) The method of claim 32, wherein the $\alpha_4\beta_1$ -integrin antagonist is ELND001.

34. (Previously Presented) The method of claim 31, wherein the effective average particle size of the nanoparticulate α -integrin antagonist particles is selected from the group consisting of less than 1900 nm, less than 1800 nm, less than 1700 nm, less than 1600 nm, less than 1500 nm, less than 1400 nm, less than 1300 nm, less than 1200 nm, less than 1100 nm, less than 1000 nm, less than 900 nm, less than 800 nm, less than 700 nm, less than 600 nm, less than 500 nm, less than 400 nm, less than 300 nm, less than 250 nm, less than 200 nm, less than 150 nm, less than 100 nm, less than 75 nm, and less than 50 nm.

35. (Original) The method of claim 31 wherein the subject in need is suffering from an inflammatory disease.

36. (New) The composition of claim 1, wherein the composition is formulated into a dosage form selected from the group consisting of liquid dispersions, gels, aerosols, ointments, creams, tablets, and capsules.

37. (New) The composition of claim 1, wherein the composition is formulated into a dosage form selected from the group consisting of lyophilized formulations, fast melt formulations, controlled release formulations, delayed release formulations, extended release formulations, pulsatile release formulations, and mixed immediate release and controlled release formulations.

AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions of claims in the application.

1. (Currently Amended) A sterile, low viscosity liquid dosage form comprising:
 - (a) particles of at least one active agent;
 - (b) at least one surface stabilizer; and
 - (c) at least one pharmaceutically acceptable excipient, carrier, or a combination thereof,wherein:
 - (i) the active agent particles have an effective average particle size of less than about ~~2 microns and~~ 200 nm,
 - (ii) the dosage form has a viscosity of less than about 2000 mPa·s at a shear rate of 0.1 (1/s), and
 - (iii) the dosage form is sterilized by passing through a filter having a pore size of about 0.2 microns.
2. (Original) The dosage form of claim 1 having a viscosity at a shear rate of 0.1 (1/s) selected from the group consisting of from about 2000 mPa·s to about 1 mPa·s, from about 1900 mPa·s to about 1 mPa·s, from about 1800 mPa·s to about 1 mPa·s, from about 1700 mPa·s to about 1 mPa·s, from about 1600 mPa·s to about 1 mPa·s, from about 1500 mPa·s to about 1 mPa·s, from about 1400 mPa·s to about 1 mPa·s, from about 1300 mPa·s to about 1 mPa·s, from about 1200 mPa·s to about 1 mPa·s, from about 1100 mPa·s to about 1 mPa·s, from about 1000 mPa·s to about 1 mPa·s, from about 900 mPa·s to about 1 mPa·s, from about 800 mPa·s to about 1 mPa·s, from about 700 mPa·s to about 1 mPa·s, from about 600 mPa·s to about 1 mPa·s, from about 500 mPa·s to about 1 mPa·s, from about 400 mPa·s to about 1 mPa·s, from about 300 mPa·s to about 1 mPa·s, from about 200 mPa·s to about 1 mPa·s, from about 175 mPa·s to about 1 mPa·s, from about 150 mPa·s to about 1 mPa·s, from about 125 mPa·s to about 1 mPa·s, from

about 100 mPa·s to about 1 mPa·s, from about 75 mPa·s to about 1 mPa·s, from about 50 mPa·s to about 1 mPa·s, from about 25 mPa·s to about 1 mPa·s, from about 15 mPa·s to about 1 mPa·s, from about 10 mPa·s to about 1 mPa·s, and from about 5 mPa·s to about 1 mPa·s.

3.-5. (Cancelled)

6. (Original) The dosage form of claim 1 formulated for administration selected from the group consisting of oral, pulmonary, rectal, ophthalmic, colonic, parenteral, intracisternal, intravenous, intravaginal, intraperitoneal, local, buccal, nasal, and topical administration.

7. (Original) The dosage form of claim 1 suitable for administration in a form selected from the group consisting of controlled release administration, fast melt administration, and aerosol administration.

8. (Currently Amended) The dosage form of claim 1, wherein the effective average particle size of the active agent is selected from the group consisting of ~~less than about 1900 nm, less than about 1800 nm, less than about 1700 nm, less than about 1600 nm, less than about 1500 nm, less than about 1400 nm, less than about 1300 nm, less than about 1200 nm, less than about 1100 nm, less than about 1000 nm, less than about 900 nm, less than about 800 nm, less than about 700 nm, less than about 600 nm, less than about 500 nm, less than about 400 nm, less than about 300 nm, less than about 250 nm, less than about 200 nm,~~ less than about 100 nm, less than about 75 nm, and less than about 50 nm.

9. (Previously Presented) The dosage form of claim 1, wherein at least about 70%, about 90%, or about 95% of the active agent particles have a particle size less than the effective average particle size.

10. (Original) The dosage form of claim 1, wherein said active agent is water-soluble.
11. (Original) The dosage form of claim 1, wherein said active agent is poorly water-soluble.
12. (Currently Amended) The dosage form of claim 1, wherein the active agent is in the form of crystalline particles, semi-crystalline particles, or amorphous particles, ~~semi-amorphous particles, or a mixture thereof.~~
13. (Original) The dosage form of claim 1, wherein the active agent is present in an amount selected from the group consisting of from about 99.5% to about 0.001%, from about 95% to about 0.1%, and from about 90% to about 0.5%, by weight, based on the total combined weight of the at least one active agent and at least one surface stabilizer, not including other excipients.
14. (Original) The dosage form of claim 1, wherein the at least one active agent is selected from the group consisting of COX-2 inhibitors, anticancer agents, NSAIDS, proteins, peptides, nutraceuticals, anti-obesity agents, corticosteroids, elastase inhibitors, analgesics, anti-fungals, oncology therapies, anti-emetics, analgesics, cardiovascular agents, anti-inflammatory agents, anthelmintics, anti-arrhythmic agents, antibiotics, anticoagulants, antidepressants, antidiabetic agents, antiepileptics, antihistamines, antihypertensive agents, antimuscarinic agents, antimycobacterial agents, antineoplastic agents, immunosuppressants, antithyroid agents, antiviral agents, anxiolytics, sedatives, astringents, beta-adrenoceptor blocking agents, blood products and substitutes, cardiac inotropic agents, contrast media, cough suppressants, diagnostic agents, diagnostic imaging agents, diuretics, dopaminergics, haemostatics, immunological agents, lipid regulating agents, muscle relaxants, parasympathomimetics, parathyroid calcitonin and

biphosphonates, prostaglandins, radio-pharmaceuticals, sex hormones, anti-allergic agents, stimulants and anoretics, sympathomimetics, thyroid agents, vasodilators, xanthines, acne medication, alpha-hydroxy formulations, cystic-fibrosis therapies, asthma therapies, emphysema therapies, respiratory distress syndrome therapies, chronic bronchitis therapies, chronic obstructive pulmonary disease therapies, organ-transplant rejection therapies, therapies for tuberculosis and other infections of the lung, and respiratory illness therapies associated with acquired immune deficiency syndrome.

15. (Original) The dosage form of claim 14, wherein the nutraceutical is selected from the group consisting of dietary supplements, vitamins, minerals, herbs, healing foods that have medical or pharmaceutical effects on the body, folic acid, fatty acids, fruit and vegetable extracts, vitamin supplements, mineral supplements, phosphatidylserine, lipoic acid, melatonin, glucosamine/chondroitin, Aloe Vera, Guggul, glutamine, amino acids, green tea, lycopene, whole foods, food additives, herbs, phytonutrients, antioxidants, flavonoid constituents of fruits, evening primrose oil, flax seeds, fish and marine animal oils, and probiotics.

16. (Original) The dosage form of claim 1, comprising at least two surface stabilizers.

17. (Original) The dosage form of claim 1, wherein the at least one surface stabilizer is present in an amount selected from the group consisting of from about 0.5% to about 99.999%, from about 5.0% to about 99.9%, and from about 10% to about 99.5%, by weight, based on the total combined dry weight of the at least one active agent and at least one surface stabilizer, not including other excipients.

18. (Original) The dosage form of claim 1, wherein the at least one surface stabilizer is selected from the group consisting of an anionic surface stabilizer, a cationic surface stabilizer, an ionic surface stabilizer, and a zwitterionic surface stabilizer.

19. (Original) The dosage form of claim 18, wherein the at least one surface stabilizer is selected from the group consisting of cetyl pyridinium chloride, gelatin, casein, phosphatides, dextran, glycerol, gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glycerol monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers, polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters, polyethylene glycols, dodecyl trimethyl ammonium bromide, polyoxyethylene stearates, colloidal silicon dioxide, phosphates, sodium dodecylsulfate, carboxymethylcellulose calcium, hydroxypropyl celluloses, hydroxypropyl methylcellulose, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hydroxypropylmethylcellulose phthalate, noncrystalline cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol, polyvinylpyrrolidone, 4-(1,1,3,3-tetramethylbutyl)-phenol polymer with ethylene oxide and formaldehyde, poloxamers; poloxamines, a charged phospholipid, dioctylsulfosuccinate, dialkylesters of sodium sulfosuccinic acid, sodium lauryl sulfate, alkyl aryl polyether sulfonates, mixtures of sucrose stearate and sucrose distearate, p-isononylphenoxypoly-(glycidol), decanoyl-N-methylglucamide; n-decyl β -D-glucopyranoside; n-decyl β -D-maltopyranoside; n-dodecyl β -D-glucopyranoside; n-dodecyl β -D-maltoside; heptanoyl-N-methylglucamide; n-heptyl- β -D-glucopyranoside; n-heptyl β -D-thioglucoside; n-hexyl β -D-glucopyranoside; nonanoyl-N-methylglucamide; n-nonyl β -D-glucopyranoside; octanoyl-N-methylglucamide; n-octyl- β -D-glucopyranoside; octyl β -D-thioglucopyranoside; lysozyme, PEG-derivatized phospholipid, PEG-derivatized cholesterol, PEG-derivatized cholesterol derivative, PEG-derivatized vitamin A, PEG-derivatized vitamin E, and random copolymers of vinyl acetate and vinyl pyrrolidone.

20. (Original) The dosage form of claim 18, wherein the at least one cationic surface stabilizer is selected from the group consisting of a polymer, a biopolymer, a polysaccharide, a cellulosic, an alginate, a nonpolymeric compound, a phospholipid, zwitterionic stabilizers, poly-

n-methylpyridinium, anthryl pyridinium chloride, chitosan, polylysine, polyvinylimidazole, polybrene, polymethylmethacrylate trimethylammoniumbromide bromide (PMMTMABr), hexyldesyltrimethylammonium bromide (HDMAB), polyvinylpyrrolidone-2-dimethylaminoethyl methacrylate dimethyl sulfate, 1,2 Dipalmitoyl-sn-Glycero-3-Phosphoethanolamine-N-[Amino(Polyethylene Glycol)2000] (sodium salt), Poly(2-methacryloxyethyl trimethylammonium bromide), poloxamines, lysozyme, alginic acid, carrageenan, and POLYOX.

Claims 21-82 (Cancelled).

WHAT IS CLAIMED IS:

1. A stable nanoparticulate nanoparticulate kinase inhibitor composition comprising:
 - (a) particles of LS104 or a salt or derivative thereof having an effective average particle size of less than about 2000 nm; and
 - (b) at least one surface stabilizer.
2. The composition of claim 1, wherein the LS104 is in a crystalline phase, an amorphous phase, a semi-crystalline phase, a semi amorphous phase, or mixtures thereof.
3. The composition of claim 1, wherein the effective average particle size of the particles of LS104 or a salt or derivative thereof is selected from the group consisting of less than about 1900 nm, less than about 1800 nm, less than about 1700 nm, less than about 1600 nm, less than about 1500 nm, less than about 1400 nm, less than about 1300 nm, less than about 1200 nm, less than about 1100 nm, less than about 1000 nm, less than about 990 nm, less than about 980 nm, less than about 970 nm, less than about 960 nm, less than about 950 nm, less than about 940 nm, less than about 930 nm, less than about 920 nm, less than about 910 nm, less than about 900 nm, less than about 890 nm, less than about 880 nm, less than about 870 nm, less than about 860 nm, less than about 850 nm, less than about 840 nm, less than about 830 nm, less than about 820 nm, less than about 810 nm, less than about 800 nm, less than about 790 nm, less than about 780 nm, less than about 770 nm, less than about 760 nm, less than about 750 nm, less than about 740 nm, less than about 730 nm, less than about 720 nm, less than about 710 nm, less than about 700 nm, less than about 690 nm, less than about 680 nm, less than about 670 nm, less than about 660 nm, less than about 650 nm, less than about 640 nm, less than about 630 nm, less than about 620 nm, less than about 610 nm, less than about 600 nm, less than about 590 nm, less than about 580 nm, less than about 570 nm, less than about 560 nm, less than about 550 nm, less than about 540 nm, less than about 530 nm, less than about 520 nm, less than about 510 nm, less than about 500 nm, less than about 490 nm, less than about 480 nm, less than about 470 nm, less than about 460 nm, less than about 450 nm, less than about 440 nm, less than about 430 nm, less than about 420 nm, less than about 410 nm, less than about 400 nm, less than about 390 nm, less than about 380 nm, less than about 370 nm, less than about 360 nm, less than about 350 nm, less than about 340 nm, less than about 330 nm, less than about 320 nm, less than about 310 nm, less than about

300 nm, less than about 290 nm, less than about 280 nm, less than about 270 nm, less than about 260 nm, less than about 250 nm, less than about 240 nm, less than about 230 nm, less than about 220 nm, less than about 210 nm, less than about 200 nm, less than about 190 nm, less than about 180 nm, less than about 170 nm, less than about 160 nm, less than about 150 nm, less than about 140 nm, less than about 130 nm, less than about 120 nm, less than about 110 nm, less than about 100, less than about 75 nm, and less than about 50 nm.

4. The composition of claim 1, wherein the nanoparticulate LS104 composition has improved bioavailability as compared to conventional LS104 compositions.
5. The composition of claim 1, wherein the composition is formulated:
 - (a) for administration selected from the group consisting of oral, pulmonary, intravenous, rectal, ophthalmic, colonic, parenteral, intracisternal, intravaginal, intraperitoneal, local, buccal, nasal, and topical administration;
 - (b) into a dosage form selected from the group consisting of liquid dispersions, gels, aerosols, ointments, creams, tablets, sachets and capsules;
 - (c) into a dosage form selected from the group consisting of lyophilized formulations, fast melt formulations, controlled release formulations, delayed release formulations, extended release formulations, pulsatile release formulations, and mixed immediate release and controlled release formulations; or
 - (d) any combination of (a), (b), and (c).
6. The composition of claim 1, wherein the composition further comprises one or more pharmaceutically acceptable excipients, carriers, or a combination thereof.
7. The composition of claim 1, wherein:
 - (a) the amount of LS104 is selected from the group consisting of from about 99.5% to about 0.001%, from about 95% to about 0.1%, and from about 90% to about 0.5%, by weight, based on the total combined dry weight of LS104 and at least one surface stabilizer, not including other excipients;
 - (b) at least one surface stabilizer is present in an amount selected from the group consisting 0.01% to about 99.5% by weight, from about 0.1% to about 95% by weight, from about 0.5% to about 90% by weight, from about 5.0% to about 99.9% by weight, and from about 10% to about 99.5% by weight, based on the total combined dry weight of LS104 and at least one surface stabilizer, not including other excipients; or

(c) a combination of (a) and (b).

8. The composition of claim 1, comprising at least one primary surface stabilizer and at least one secondary surface stabilizer.

9. The composition of claim 1, wherein at least one surface stabilizer is selected from the group consisting of a non-ionic surface stabilizer, an ionic surface stabilizer, an anionic surface stabilizer, a cationic surface stabilizer, and a zwitterionic surface stabilizer.

10. The composition of claim 1, wherein at least one surface stabilizer is selected from the group consisting of albumin, human serum albumin, bovine serum albumin, cetyl pyridinium chloride, gelatin, casein, phosphatides, dextran, glycerol, gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glycerol monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers, polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters, polyethylene glycols, dodecyl trimethyl ammonium bromide, polyoxyethylene stearates, colloidal silicon dioxide, phosphates, sodium dodecylsulfate, carboxymethylcellulose calcium, hydroxypropyl celluloses, hypromellose, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hypromellose phthalate, noncrystalline cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol, polyvinylpyrrolidone, 4-(1,1,3,3-tetramethylbutyl)-phenol polymer with ethylene oxide and formaldehyde, poloxamers; poloxamines, a charged phospholipid, dioctylsulfosuccinate, dialkylesters of sodium sulfosuccinic acid, sodium lauryl sulfate, alkyl aryl polyether sulfonates, mixtures of sucrose stearate and sucrose distearate, $C_{18}H_{37}CH_2C(O)N(CH_3)-CH_2(CHOH)_4(CH_2OH)_2$, p-isononylphenoxypoly-(glycidol), decanoyl-N-methylglucamide; n-decyl β -D-glucopyranoside; n-decyl β -D-maltopyranoside; n-dodecyl β -D-glucopyranoside; n-dodecyl β -D-maltoside; heptanoyl-N-methylglucamide; n-heptyl- β -D-glucopyranoside; n-heptyl β -D-thioglucoside; n-hexyl β -D-glucopyranoside; nonanoyl-N-methylglucamide; n-nonyl β -D-glucopyranoside; octanoyl-N-methylglucamide; n-octyl- β -D-glucopyranoside; octyl β -D-thioglucopyranoside; lysozyme, PEG-phospholipid, PEG-cholesterol, PEG-cholesterol derivative, lysozyme, PEG-vitamin A, PEG-vitamin E, random copolymers of vinyl acetate and vinyl pyrrolidone, a cationic polymer, a cationic biopolymer, a cationic polysaccharide, a cationic cellulosic, a cationic alginate, a cationic nonpolymeric compound, a cationic phospholipid, cationic lipids, polymethylmethacrylate trimethylammonium bromide,

sulfonium compounds, polyvinylpyrrolidone-2-dimethylaminoethyl methacrylate dimethyl sulfate, hexadecyltrimethyl ammonium bromide, phosphonium compounds, quaternary ammonium compounds, benzyl-di(2-chloroethyl)ethylammonium bromide, coconut trimethyl ammonium chloride, coconut trimethyl ammonium bromide, coconut methyl dihydroxyethyl ammonium chloride, coconut methyl dihydroxyethyl ammonium bromide, decyl triethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride bromide, C₁₂₋₁₅dimethyl hydroxyethyl ammonium chloride, C₁₂₋₁₅dimethyl hydroxyethyl ammonium chloride bromide, coconut dimethyl hydroxyethyl ammonium chloride, coconut dimethyl hydroxyethyl ammonium bromide, myristyl trimethyl ammonium methyl sulphate, lauryl dimethyl benzyl ammonium chloride, lauryl dimethyl benzyl ammonium bromide, lauryl dimethyl (ethenoxy)₄ ammonium chloride, lauryl dimethyl (ethenoxy)₄ ammonium bromide, N-alkyl (C₁₂₋₁₈)dimethylbenzyl ammonium chloride, N-alkyl (C₁₄₋₁₈)dimethyl-benzyl ammonium chloride, N-tetradecyldimethylbenzyl ammonium chloride monohydrate, dimethyl didecyl ammonium chloride, N-alkyl and (C₁₂₋₁₄) dimethyl 1-naphthylmethyl ammonium chloride, trimethylammonium halide, alkyl-trimethylammonium salts, dialkyl-dimethylammonium salts, lauryl trimethyl ammonium chloride, ethoxylated alkyamidoalkyldialkylammonium salt, an ethoxylated trialkyl ammonium salt, dialkylbenzene dialkylammonium chloride, N-didecyldimethyl ammonium chloride, N-tetradecyldimethylbenzyl ammonium, chloride monohydrate, N-alkyl(C₁₂₋₁₄) dimethyl 1-naphthylmethyl ammonium chloride, dodecyldimethylbenzyl ammonium chloride, dialkyl benzenealkyl ammonium chloride, lauryl trimethyl ammonium chloride, alkylbenzyl methyl ammonium chloride, alkyl benzyl dimethyl ammonium bromide, C₁₂ trimethyl ammonium bromides, C₁₅ trimethyl ammonium bromides, C₁₇ trimethyl ammonium bromides, dodecylbenzyl triethyl ammonium chloride, poly-diallyldimethylammonium chloride (DADMAC), dimethyl ammonium chlorides, alkyldimethylammonium halogenides, tricetyl methyl ammonium chloride, decyltrimethylammonium bromide, dodecyltriethylammonium bromide, tetradecyltrimethylammonium bromide, methyl trioctylammonium chloride, POLYQUAT 10™, tetrabutylammonium bromide, benzyl trimethylammonium bromide, choline esters, benzalkonium chloride, stearylalkonium chloride compounds, cetyl pyridinium bromide, cetyl pyridinium chloride, halide salts of quaternized polyoxyethylalkylamines, MIRAPOL™, ALKAQUAT™, alkyl pyridinium salts; amines, amine salts, amine oxides, imide azolinium salts, protonated quaternary acrylamides, methylated quaternary polymers, and cationic guar.

11. The composition of claim 1, additionally comprising one or more active agents useful for the treatment of cell proliferative diseases or disorders.

12. The composition of claim 1, wherein:

(a) upon administration to a mammal the particles of LS104 or a salt or derivative thereof redisperse such that the particles have an effective average particle size selected from the group consisting of less than about 2 microns, less than about 1900 nm, less than about 1800 nm, less than about 1700 nm, less than about 1600 nm, less than about 1500 nm, less than about 1400 nm, less than about 1300 nm, less than about 1200 nm, less than about 1100 nm, less than about 1000 nm, less than about 990 nm, less than about 980 nm, less than about 970 nm, less than about 960 nm, less than about 950 nm, less than about 940 nm, less than about 930 nm, less than about 920 nm, less than about 910 nm, less than about 900 nm, less than about 890 nm, less than about 880 nm, less than about 870 nm, less than about 860 nm, less than about 850 nm, less than about 840 nm, less than about 830 nm, less than about 820 nm, less than about 810 nm, less than about 800 nm, less than about 790 nm, less than about 780 nm, less than about 770 nm, less than about 760 nm, less than about 750 nm, less than about 740 nm, less than about 730 nm, less than about 720 nm, less than about 710 nm, less than about 700 nm, less than about 690 nm, less than about 680 nm, less than about 670 nm, less than about 660 nm, less than about 650 nm, less than about 640 nm, less than about 630 nm, less than about 620 nm, less than about 610 nm, less than about 600 nm, less than about 590 nm, less than about 580 nm, less than about 570 nm, less than about 560 nm, less than about 550 nm, less than about 540 nm, less than about 530 nm, less than about 520 nm, less than about 510 nm, less than about 500 nm, less than about 490 nm, less than about 480 nm, less than about 470 nm, less than about 460 nm, less than about 450 nm, less than about 440 nm, less than about 430 nm, less than about 420 nm, less than about 410 nm, less than about 400 nm, less than about 390 nm, less than about 380 nm, less than about 370 nm, less than about 360 nm, less than about 350 nm, less than about 340 nm, less than about 330 nm, less than about 320 nm, less than about 310 nm, less than about 300 nm, less than about 290 nm, less than about 280 nm, less than about 270 nm, less than about 260 nm, less than about 250 nm, less than about 240 nm, less than about 230 nm, less than about 220 nm, less than about 210 nm, less than about 200 nm, less than about 190 nm, less than about 180 nm, less than about 170 nm, less than about 160 nm, less than about 150 nm, less than about 140 nm, less than about 130 nm, less than about 120 nm, less than about 110 nm, less than about 100, less than about 75 nm, and less than about 50 nm;

(b) the composition redisperses in a biorelevant medium such that the LS104 particles have an effective average particle size selected from the group consisting of less than about 2 microns, less than about 1900 nm, less than about 1800 nm, less than about 1700 nm, less than about 1600 nm, less than about 1500 nm, less than about 1400 nm, less than about 1300 nm, less than about 1200 nm, less than about 1100 nm, less than about 1000 nm, less than about 990 nm, less than about 980 nm, less than about 970 nm, less than about 960 nm, less than about 950 nm, less than about 940 nm, less than about 930 nm, less than about 920 nm, less than about 910 nm, less than about 900 nm, less than about 890 nm, less than about 880 nm, less than about 870 nm, less than about 860 nm, less than about 850 nm, less than about 840 nm, less than about 830 nm, less than about 820 nm, less than about 810 nm, less than about 800 nm, less than about 790 nm, less than about 780 nm, less than about 770 nm, less than about 760 nm, less than about 750 nm, less than about 740 nm, less than about 730 nm, less than about 720 nm, less than about 710 nm, less than about 700 nm, less than about 690 nm, less than about 680 nm, less than about 670 nm, less than about 660 nm, less than about 650 nm, less than about 640 nm, less than about 630 nm, less than about 620 nm, less than about 610 nm, less than about 600 nm, less than about 590 nm, less than about 580 nm, less than about 570 nm, less than about 560 nm, less than about 550 nm, less than about 540 nm, less than about 530 nm, less than about 520 nm, less than about 510 nm, less than about 500 nm, less than about 490 nm, less than about 480 nm, less than about 470 nm, less than about 460 nm, less than about 450 nm, less than about 440 nm, less than about 430 nm, less than about 420 nm, less than about 410 nm, less than about 400 nm, less than about 390 nm, less than about 380 nm, less than about 370 nm, less than about 360 nm, less than about 350 nm, less than about 340 nm, less than about 330 nm, less than about 320 nm, less than about 310 nm, less than about 300 nm, less than about 290 nm, less than about 280 nm, less than about 270 nm, less than about 260 nm, less than about 250 nm, less than about 240 nm, less than about 230 nm, less than about 220 nm, less than about 210 nm, less than about 200 nm, less than about 190 nm, less than about 180 nm, less than about 170 nm, less than about 160 nm, less than about 150 nm, less than about 140 nm, less than about 130 nm, less than about 120 nm, less than about 110 nm, less than about 100, less than about 75 nm, and less than about 50 nm; or

(c) a combination of (a) and (b).

13. The composition of claim 12, wherein the biorelevant medium is selected from the group consisting of water, aqueous electrolyte solutions, aqueous solutions of a salt, aqueous solutions of an acid, aqueous solutions of a base, and combinations thereof.

14. The composition of claim 1, wherein:

- (a) the T_{\max} of the nanoparticulate LS104 composition, when assayed in the plasma of a mammalian subject following administration, is less than the T_{\max} for a non-nanoparticulate composition of the same LS104, administered at the same dosage;
- (b) the C_{\max} of the nanoparticulate LS104 composition, when assayed in the plasma of a mammalian subject following administration, is greater than the C_{\max} for a non-nanoparticulate composition of the same LS104, administered at the same dosage;
- (c) the AUC of the nanoparticulate LS104 composition, when assayed in the plasma of a mammalian subject following administration, is greater than the AUC for a non-nanoparticulate composition of the same LS104, administered at the same dosage; or
- (d) any combination of (a), (b) and (c).

15. The composition of claim 14, wherein:

- (a) the T_{\max} is selected from the group consisting of not greater than about 90%, not greater than about 80%, not greater than about 70%, not greater than about 60%, not greater than about 50%, not greater than about 30%, not greater than about 25%, not greater than about 20%, not greater than about 15%, not greater than about 10%, and not greater than about 5% of the T_{\max} exhibited by a non-nanoparticulate composition of the same LS104, administered at the same dosage;
- (b) the C_{\max} is selected from the group consisting of at least about 50%, at least about 100%, at least about 200%, at least about 300%, at least about 400%, at least about 500%, at least about 600%, at least about 700%, at least about 800%, at least about 900%, at least about 1000%, at least about 1100%, at least about 1200%, at least about 1300%, at least about 1400%, at least about 1500%, at least about 1600%, at least about 1700%, at least about 1800%, or at least about 1900% greater than the C_{\max} exhibited by a non-nanoparticulate composition of the same LS104, administered at the same dosage;
- (c) the AUC is selected from the group consisting of at least about 25%, at least about 50%, at least about 75%, at least about 100%, at least about 125%, at least about 150%, at least about 175%, at least about 200%, at least about 225%, at least about 250%, at least about 275%, at least about 300%, at least about 350%, at least about 400%, at least about

450%, at least about 500%, at least about 550%, at least about 600%, at least about 750%, at least about 700%, at least about 750%, at least about 800%, at least about 850%, at least about 900%, at least about 950%, at least about 1000%, at least about 1050%, at least about 1100%, at least about 1150%, or at least about 1200% greater than the AUC exhibited by the non-nanoparticulate formulation of the same LS104, administered at the same dosage; or

(d) any combination of (a), (b), and (c).

16. The composition of claim 1 which does not produce significantly different absorption levels when administered under fed as compared to fasting conditions.

17. The composition of claim 16, wherein the difference in absorption of the active agent composition of the invention, when administered in the fed versus the fasted state, is selected from the group consisting of less than about 100%, less than about 90%, less than about 80%, less than about 70%, less than about 60%, less than about 50%, less than about 40%, less than about 30%, less than about 25%, less than about 20%, less than about 15%, less than about 10%, less than about 5%, and less than about 3%.

18. The composition of claim 1, wherein administration of the composition to a human in a fasted state is bioequivalent to administration of the composition to a subject in a fed state.

19. The composition of claim 18, wherein "bioequivalency" is established by:

(a) a 90% Confidence Interval of between 0.80 and 1.25 for both C_{max} and AUC;

or

(b) a 90% Confidence Interval of between 0.80 and 1.25 for AUC and a 90% Confidence Interval of between 0.70 to 1.43 for C_{max} .

19. A method of making a nanoparticulate LS104, or a salt or derivative thereof, composition comprising contacting particles of an LS104 with at least one surface stabilizer for a time and under conditions sufficient to provide a nanoparticulate LS104 composition having an effective average particle size of less than about 2000 nm.

20. The method of claim 19, wherein the contacting comprises milling, wet milling, homogenizing, precipitation, freezing, supercritical fluid particle generation techniques, emulsion techniques, nano-electrospray techniques, or any combination thereof.

21. A method of treating a mammal in need comprising administering a stable nanoparticulate nanoparticulate kinase inhibitor composition comprising:
- (a) particles of LS104 or a salt or derivative thereof having an effective average particle size of less than about 2000 nm; and
 - (b) at least one surface stabilizer.
22. The method of claim 21, wherein the medicament is useful in treating leukemia, myeloproliferative diseases and related diseases or disorders.

AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions of claims in the application.

1. (Previously Presented) A stable nanoparticulate α -integrin antagonist composition comprising:
 - (a) particles of at least one α -integrin antagonist or a salt thereof having an effective average particle size of less than 2000 nm; and
 - (b) at least one surface stabilizer,wherein said surface stabilizer is not copolymers of vinyl pyrrolidone and vinyl acetate.
2. (Original) The composition of claim 1, wherein the nanoparticulate α -integrin antagonist is an $\alpha_4\beta_1$ -integrin antagonist.
3. (Original) The composition of claim 2, wherein the $\alpha_4\beta_1$ -integrin antagonist is ELND001.
4. (Previously Presented) The α -integrin antagonist of claim 1, wherein the α -integrin antagonist is in a crystalline phase, a semi-crystalline phase, or an amorphous phase.
5. (Previously Presented) The composition of claim 1, wherein the effective average particle size of the nanoparticulate α -integrin antagonist particles is selected from the group consisting of less than 1900 nm, less than 1800 nm, less than 1700 nm, less than 1600 nm, less than 1500 nm, less than 1400 nm, less than 1300 nm, less than 1200 nm, less than 1100 nm, less than 1000 nm, less than 900 nm, less than 800 nm, less than 700 nm, less than 650 nm, less than 600 nm, less than 550 nm, less than 500 nm, less than 450 nm, less than 400 nm, less than 350 nm, less than 300 nm, less than 250 nm, less than 200 nm, less than 150 nm, less than 100 nm, less than 75 nm, or less than 50 nm.

6. (Previously Presented) The composition of claim 1, wherein the composition is formulated for administration selected from the group consisting of oral, pulmonary, intra-venous, rectal, ophthalmic, colonic, parenteral, intracisternal, intravaginal, intraperitoneal, local, buccal, nasal, and topical administration.

7. (Original) The composition of claim 1, wherein the composition further comprises one or more pharmaceutically acceptable excipients, carriers, or a combination thereof.

8. (Previously Presented) The composition of claim 1 wherein:

(a) the amount of the α -integrin antagonist is selected from the group consisting of from 99.5% to 0.001%, from 95% to 0.1%, and from 90% to 0.5%, by weight, based on the total combined weight of the α -integrin antagonist and at least one surface stabilizer, not including other excipients;

(b) at least one surface stabilizer is present in an amount selected from the group consisting of from 0.01% to 99.5% by weight, from 0.1% to 95% by weight, and from 0.5% to 90% by weight, based on the total combined dry weight of the α -integrin antagonist and the at least one surface stabilizer, not including other excipients; or

(c) a combination of (a) and (b).

9. (Original) The composition of claim 1, wherein the surface stabilizer is selected from the group consisting of an ionic surface stabilizer, a non-ionic surface stabilizer, an anionic surface stabilizer, a cationic surface stabilizer, and a zwitterionic surface stabilizer.

10. (Previously Presented) The composition of claim 1, wherein at least one surface stabilizer is selected from the group consisting of cetyl pyridinium chloride, gelatin, casein, phosphatides, dextran, glycerol, gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glycerol monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers, polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters, polyethylene glycols, dodecyl trimethyl ammonium bromide, polyoxyethylene stearates, colloidal silicon dioxide, phosphates, sodium dodecylsulfate,

carboxymethylcellulose calcium, hydroxypropyl celluloses, hydroxypropyl methylcellulose, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hydroxypropylmethylcellulose phthalate, noncrystalline cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol, polyvinylpyrrolidone, 4-(1,1,3,3-tetramethylbutyl)-phenol polymer with ethylene oxide and formaldehyde, poloxamers; poloxamines, a charged phospholipid, dioctylsulfosuccinate, dialkylesters of sodium sulfosuccinic acid, sodium lauryl sulfate, alkyl aryl polyether sulfonates, mixtures of sucrose stearate and sucrose distearate, $C_{18}H_{37}CH_2C(O)N(CH_3)-CH_2(CHOH)_4(CH_2OH)_2$, p-isononylphenoxypoly-(glycidol), decanoyl-N-methylglucamide; n-decyl β -D-glucopyranoside; n-decyl β -D-maltopyranoside; n-dodecyl β -D-glucopyranoside; n-dodecyl β -D-maltoside; heptanoyl-N-methylglucamide; n-heptyl- β -D-glucopyranoside; n-heptyl β -D-thioglucoside; n-hexyl β -D-glucopyranoside; nonanoyl-N-methylglucamide; n-nonyl β -D-glucopyranoside; octanoyl-N-methylglucamide; n-octyl- β -D-glucopyranoside; octyl β -D-thioglucopyranoside; lysozyme, PEG-phospholipid, PEG-cholesterol, PEG-cholesterol derivative, PEG-vitamin A, PEG-vitamin E, lysozyme, a cationic polymer, a cationic biopolymer, a cationic polysaccharide, a cationic cellulosic, a cationic alginate, a cationic nonpolymeric compound, a cationic phospholipids, cationic lipids, polymethylmethacrylate trimethylammonium bromide, sulfonium compounds, polyvinylpyrrolidone-2-dimethylaminoethyl methacrylate dimethyl sulfate, hexadecyltrimethyl ammonium bromide, phosphonium compounds, quaternary ammonium compounds, benzyl-di(2-chloroethyl)ethylammonium bromide, coconut trimethyl ammonium chloride, coconut trimethyl ammonium bromide, coconut methyl dihydroxyethyl ammonium chloride, coconut methyl dihydroxyethyl ammonium bromide, decyl triethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride bromide, C_{12-15} dimethyl hydroxyethyl ammonium chloride, C_{12-15} dimethyl hydroxyethyl ammonium chloride bromide, coconut dimethyl hydroxyethyl ammonium chloride, coconut dimethyl hydroxyethyl ammonium bromide, myristyl trimethyl ammonium methyl sulphate, lauryl dimethyl benzyl ammonium chloride, lauryl dimethyl benzyl ammonium bromide, lauryl

dimethyl (ethenoxy)₄ ammonium chloride, lauryl dimethyl (ethenoxy)₄ ammonium bromide, N-alkyl (C₁₂₋₁₈)dimethylbenzyl ammonium chloride, N-alkyl (C₁₄₋₁₈)dimethyl-benzyl ammonium chloride, N-tetradecyldimethylbenzyl ammonium chloride monohydrate, dimethyl didecyl ammonium chloride, N-alkyl and (C₁₂₋₁₄) dimethyl 1-naphthylmethyl ammonium chloride, trimethylammonium halide, alkyl-trimethylammonium salts, dialkyl-dimethylammonium salts, lauryl trimethyl ammonium chloride, ethoxylated alkyamidoalkyldialkylammonium salt, an ethoxylated trialkyl ammonium salt, dialkylbenzene dialkylammonium chloride, N-didecyldimethyl ammonium chloride, N-tetradecyldimethylbenzyl ammonium, chloride monohydrate, N-alkyl(C₁₂₋₁₄) dimethyl 1-naphthylmethyl ammonium chloride, dodecyldimethylbenzyl ammonium chloride, dialkyl benzenealkyl ammonium chloride, lauryl trimethyl ammonium chloride, alkylbenzyl methyl ammonium chloride, alkyl benzyl dimethyl ammonium bromide, C₁₂ trimethyl ammonium bromides, C₁₅ trimethyl ammonium bromides, C₁₇ trimethyl ammonium bromides, dodecylbenzyl triethyl ammonium chloride, poly-diallyldimethylammonium chloride (DADMAC), dimethyl ammonium chlorides, alkyldimethylammonium halogenides, tricetyl methyl ammonium chloride, decyltrimethylammonium bromide, dodecyltriethylammonium bromide, tetradecyltrimethylammonium bromide, methyl trioctylammonium chloride, polyquaternium 10, tetrabutylammonium bromide, benzyl trimethylammonium bromide, choline esters, benzalkonium chloride, stearalkonium chloride compounds, cetyl pyridinium bromide, cetyl pyridinium chloride, halide salts of quaternized polyoxyethylalkylamines, quaternized ammonium salt polymers, alkyl pyridinium salts; amines, amine salts, amine oxides, imide azolinium salts, protonated quaternary acrylamides, methylated quaternary polymers, and cationic guar.

11. (Previously Presented) The composition claim 1, wherein:

(a) upon administration to a mammal the α -integrin antagonist particles redisperse such that the particles have an effective average particle size selected from the group consisting of less than 2 microns, less than 1900 nm, less than 1800 nm, less than 1700 nm, less than 1600

nm, less than 1500 nm, less than 1400 nm, less than 1300 nm, less than 1200 nm, less than 1100 nm, less than 1000 nm, less than 900 nm, less than 800 nm, less than 700 nm, less than 600 nm, less than 500 nm, less than 400 nm, less than 300 nm, less than 250 nm, less than 200 nm, less than 150 nm, less than 100 nm, less than 75 nm, and less than 50 nm;

(b) the composition redisperses in a biorelevant media such that the α -integrin antagonist particles have an effective average particle size selected from the group consisting of less than 2 microns, less than 1900 nm, less than 1800 nm, less than 1700 nm, less than 1600 nm, less than 1500 nm, less than 1400 nm, less than 1300 nm, less than 1200 nm, less than 1100 nm, less than 1000 nm, less than 900 nm, less than 800 nm, less than 700 nm, less than 600 nm, less than 500 nm, less than 400 nm, less than 300 nm, less than 250 nm, less than 200 nm, less than 150 nm, less than 100 nm, less than 75 nm, and less than 50 nm; or

(c) a combination of (a) and (b).

12. (Original) The composition of claim 11, wherein the biorelevant media is selected from the group consisting of water, aqueous electrolyte solutions, aqueous solutions of a salt, aqueous solutions of an acid, aqueous solutions of a base, and combinations thereof.

13. (Original) The composition of claim 1, wherein:

(a) the T_{\max} of the α -integrin antagonist, when assayed in the plasma of a mammalian subject following administration, is less than the T_{\max} for a non-nanoparticulate composition of the same α -integrin antagonist, administered at the same dosage;

(b) the C_{\max} of the α -integrin antagonist, when assayed in the plasma of a mammalian subject following administration, is greater than the C_{\max} for a non-nanoparticulate composition of the same α -integrin antagonist, administered at the same dosage;

(c) the AUC of the α -integrin antagonist, when assayed in the plasma of a mammalian subject following administration, is greater than the AUC for a non-nanoparticulate composition of the same α -integrin antagonist, administered at the same dosage; or

(d) any combination of (a), (b), and (c).

14. (Previously Presented) The composition of claim 13, wherein:

(a) the T_{\max} is selected from the group consisting of not greater than 90%, not greater than 80%, not greater than 70%, not greater than 60%, not greater than 50%, not greater than 30%, not greater than 25%, not greater than 20%, not greater than 15%, not greater than 10%, and not greater than 5% of the T_{\max} exhibited by a non-nanoparticulate composition of the same α -integrin antagonist, administered at the same dosage;

(b) the C_{\max} is selected from the group consisting of at least 50%, at least 100%, at least 200%, at least 300%, at least 400%, at least 500%, at least 600%, at least 700%, at least 800%, at least 900%, at least 1000%, at least 1100%, at least 1200%, at least 1300%, at least 1400%, at least 1500%, at least 1600%, at least 1700%, at least 1800%, or at least 1900% greater than the C_{\max} exhibited by a non-nanoparticulate composition of the same α -integrin antagonist, administered at the same dosage;

(c) the AUC is selected from the group consisting of at least 25%, at least 50%, at least 75%, at least 100%, at least 125%, at least 150%, at least 175%, at least 200%, at least 225%, at least 250%, at least 275%, at least 300%, at least 350%, at least 400%, at least 450%, at least 500%, at least 550%, at least 600%, at least 750%, at least 700%, at least 750%, at least 800%, at least 850%, at least 900%, at least 950%, at least 1000%, at least 1050%, at least 1100%, at least 1150%, or at least 1200% greater than the AUC exhibited by the non-nanoparticulate formulation of the same α -integrin antagonist, administered at the same dosage;
or

(d) any combination of (a), (b), and (c).

15. (Previously Presented) The composition of claim 1, wherein the C_{\max} of the α -integrin antagonist, when assayed in the plasma of the mammalian subject, is selected from the group consisting of greater than 1 $\mu\text{g/mL}$, greater than 3 $\mu\text{g/mL}$, greater than 5 $\mu\text{g/mL}$, greater than 10 $\mu\text{g/mL}$, and greater than 15 $\mu\text{g/mL}$.

16. (Cancelled)

17. (Previously Presented) The composition of claim 1, wherein the difference in absorption level of the α -integrin antagonist or a salt thereof, when administered in the fed versus the fasted state, is selected from the group consisting of less than 100%, less than 90%, less than 80%, less than 70%, less than 60%, less than 50%, less than 40%, less than 30%, less than 25%, less than 20%, less than 15%, less than 10%, less than 5%, and less than 3%.

18. (Original) The composition of claim 1, wherein administration of the composition to a human in a fasted state is bioequivalent to administration of the composition to a subject in a fed state.

19. (Original) The composition of claim 18, wherein "bioequivalency" is established by:

- (a) a 90% Confidence Interval of between 0.80 and 1.25 for both C_{\max} and AUC; or
- (b) a 90% Confidence Interval of between 0.80 and 1.25 for AUC and a 90% Confidence Interval of between 0.70 to 1.43 for C_{\max} .

20. (Previously Presented) The composition of claim 1, additionally comprising a α -integrin antagonist composition having an effective average particle size which is greater than 2 microns.

21. (Previously Presented) The composition of claim 1, additionally comprising at least one additional nanoparticulate α -integrin antagonist composition, having an effective average particle size of less than 2 microns, wherein the additional nanoparticulate α -integrin antagonist composition has an effective average particle size which is different than particle size of the nanoparticulate α -integrin antagonist composition of claim 1.

22. (Original) The composition of claim 1, additionally comprising at least one non- α -integrin antagonist active agent selected from the group consisting of proteins, peptides, nucleotides, anti-obesity drugs, nutraceuticals, dietary supplements, carotenoids, corticosteroids,

elastase inhibitors, anti-fungals, alkylxanthine, oncology therapies, anti-emetics, analgesics, opioids, antipyretics, cardiovascular agents, anti-inflammatory agents, anthelmintics, anti-arrhythmic agents, antibiotics, anticoagulants, antidepressants, antidiabetic agents, antiepileptics, antihistamines, antihypertensive agents, antimuscarinic agents, antimycobacterial agents, antineoplastic agents, immunosuppressants, antithyroid agents, antiviral agents, anxiolytics, sedatives, astringents, beta-adrenoceptor blocking agents, blood products, blood substitutes, cardiac inotropic agents, contrast media, corticosteroids, cough suppressants, diagnostic agents, diagnostic imaging agents, diuretics, dopaminergics, haemostatics, immunological agents, lipid regulating agents, muscle relaxants, parasympathomimetics, parathyroid calcitonin and biphosphonates, prostaglandins, radio- pharmaceuticals, sex hormones, anti-allergic agents, stimulants, anoretics, sympathomimetics, thyroid agents, Mu receptor antagonists, Kappa receptor antagonists, non-narcotic analgesics, monoamine uptake inhibitors, adenosine regulating agents, cannabinoid derivatives, Substance P antagonists, neurokinin-1 receptor antagonists, and sodium channel blockers.

23. (Original) The composition of claim 22, wherein:

(a) the nutraceutical is selected from the group consisting of lutein, folic acid, fatty acids, fruit extracts, vegetable extracts, vitamin supplements, mineral supplements, phosphatidylserine, lipoic acid, melatonin, glucosamine/chondroitin, Aloe Vera, Guggul, glutamine, amino acids, green tea, lycopene, whole foods, food additives, herbs, phytonutrients, antioxidants, flavonoid constituents of fruits, evening primrose oil, flax seeds, fish oils, marine animal oils, and probiotics; or

(b) the anti-inflammatory agent is a COX-2 inhibitor selected from the group consisting of celecoxib, rofecoxib, valdecoxib, parecoxib, MK-966, etoricoxib, 4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]] benzenesulfonamide, N-(2-cyclohexyloxy-4-nitrophenyl)methane sulfonamide, methyl sulfone spiro(2.4)hept-5-ene 1, SC-57666, celecoxib, SC-558, SC-560, etodolac, 5,5-dimethyl-3-(3-fluorophenyl)-4-(4-methylsulfonyl)phenyl 2(5H)-furanone, MK-476, L-745337, L-761066, L-761000, L-748780, L-

748731, 5-Bromo-2-(4-fluorophenyl)-3-(4-(methylsulfonyl)phenyl), 1-(7-tert.-butyl-2,3-dihydro-3,3-dimethylbenzo(b)furan-5-yl)-4-cyclopropylbutan-1-one, 3-formylamino-7-methylsulfonylamino-6-phenoxy-4H-1-benzopyran-4-one, BF 389, PD 136005, PD 142893, PD 145065, flurbiprofen, nimesulide, nabumetone, flosulide, piroxicam, diclofenac, COX-189, D 1367, 4-nitro-2-phenoxyethane sulfonamide, (3-benzoyldifluoromethane sulfonamide, diflumidone), JTE-522, 4'-Acetyl-2'-(2,4-difluorophenoxy)methanesulfonamide, FK 867, FR 115068, GR 253035, RWJ 63556, RWJ 20485, ZK 38997, (E)-(5)-(3,5-di-tert-butyl-4-hydroxybenzylidene)-2-ethyl-1,2-isothiazolidine-1,1-dioxide indomethacin, CL 1004, RS 57067, RS 104894, SC 41930, SB 205312, SKB 209670, and Ono 1078; or

(c) the non- α -integrin antagonist active agent is selected from the group consisting of aceclofenac, acetaminophen, e-acetamidocaproic acid, acetaminophen, acetaminosalol, acetanilide, acetylsalicylic acid, S-adenosylmethionine, alclometacin, alfentanil, allylprodine, alminoprofen, aloxiprin, alphaprodine, aluminum bis(acetylsalicylate), amfenac, aminochlorphenoxazine, 3-amino-4-hydroxybutyric acid, 2-amino-4-picoline, aminopropyl, aminopyrine, amixetrine, ammonium salicylate, ampiroxicam, amtolmetin guacil, anileridine, antipyrine, antipyrine salicylate, antrafenine, apazone, bendazac, benorylate, benoxaprofen, benzpiperylon, benzydamine, benzylmorphine, bismoprocaine, bismoprocaine, bezitramide, bisabolol, bromfenac, p-bromoacetanilide, 5-bromosalicylic acid acetate, bromosaligenin, buclizine, buclizine acid, buclizine, buclizine, bumadizon, buprenorphine, butacetin, butibufen, butophanol, calcium acetylsalicylate, carbamazepine, carbiphen, carprofen, carsalam, chlorobutanol, chlorphenoxazine, choline salicylate, cinchophen, cinmetacin, cimetidine, clidazepam, clonitazepam, clonixin, clopirac, clove, codeine, codeine methyl bromide, codeine phosphate, codeine sulfate, cropropamide, crotetamide, desomorphine, dexoxadrol, dextromoramide, dezocine, diampromide, diclofenac sodium, difenamil, difenpiramide, diflunisal, dihydrocodeine, dihydrocodeinone enol acetate, dihydromorphine, dihydroxyaluminum acetylsalicylate, dimenoxadol, dimephtanol, dimethylthiambutene, dioxaphetyl butyrate, dipipanone, diprocetyl, dipyrone, ditazol, droxicam, emorfon, enfenamic acid, eprizole,

eptazocine, etersalate, ethenzamide, ethoheptazine, ethoxazene, ethylmethylthiambutene, ethylmorphine, etodolac, etofenamate, etonitazene, eugenol, felbinac, fenbufen, fenclozic acid, fendosal, fenoprofen, fentanyl, fentiazac, fepradinol, feprazone, floctafenine, flufenamic acid, flunoxaprofen, fluoresone, flupirtine, fluproquazone, flurbiprofen, fosfosal, gentisic acid, glafenine, glucametacin, glycol salicylate, guaiazulene, hydrocodone, hydromorphone, hydroxypethidine, ibufenac, ibuprofen, ibuproxam, imidazole salicylate, indomethacin, indoprofen, isofezolac, isoladol, isomethadone, isonixin, isoxepac, isoxicam, ketobemidone, ketoprofen, ketorolac, p-lactophenetide, lefetamine, levorphanol, lofentanil, lonazolac, lomoxicam, loxoprofen, lysine acetylsalicylate, magnesium acetylsalicylate, meclofenamic acid, mefenamic acid, meperidine, meptazinol, mesalamine, metazocine, methadone hydrochloride, methotrimeprazine, metiazinic acid, metofoline, metopon, mofebutazone, mofezolac, morazone, morphine, morphine hydrochloride, morphine sulfate, morpholine salicylate, myrophine, nabumetone, nalbuphine, 1-naphthyl salicylate, naproxen, narceine, nefopam, nicomorphine, nifenazone, niflumic acid, nimesulide, 5'-nitro-2'-propoxyacetanilide, norlevorphanol, normethadone, normorphine, norpipanone, olsalazine, opium, oxaceprol, oxametacine, oxaprozin, oxycodone, oxymorphone, oxyphenbutazone, papaveretum, paranyline, parsalimide, pentazocine, perisoxal, phenacetin, phenadoxone, phenazocine, phenazopyridine hydrochloride, phenocoll, phenoperidine, phenopyrazone, phenyl acetylsalicylate, phenylbutazone, phenyl salicylate, phenyramidol, piketoprofen, piminodine, pipebuzone, piperylone, piprofen, pirazolac, piritramide, piroxicam, pranoprofen, proglumetacin, proheptazine, promedol, propacetamol, propiram, propoxyphene, propyphenazone, proquazone, protizinic acid, ramifenazone, remifentanil, rimazolium metilsulfate, salacetamide, salicin, salicylamide, salicylamide o-acetic acid, salicylsulfuric acid, salsalte, salverine, simetride, sodium salicylate, sufentanil, sulfasalazine, sulindac, superoxide dismutase, suprofen, suxibuzone, talniflumate, tenidap, tenoxicam, terofenamate, tetrandrine, thiazolinobutazone, tiaprofenic acid, tiaramide, tilidine, tinoridine, tolfenamic acid, tolmetin, tramadol, tropesin, viminol, xenbucin, ximoprofen, zaltoprofen, and zomepirac.

24. (Previously Presented) The composition of claim 22 wherein at least one of the non- α -integrin antagonist active agents has an effective average particle size of less than 2 microns.

25. (Currently Amended) The composition of claim 22 wherein at least one of the non- $\alpha_4\beta_1$ -integrin antagonist active agents has an effective average particle size of greater than ~~about~~ 2000 nm.

26. (Previously Presented) A method of making a nanoparticulate composition comprising contacting an α -integrin antagonist active agent particles with at least one surface stabilizer for a time and under conditions sufficient to provide a nanoparticulate α -integrin antagonist composition having an effective average particle size of less than 2000 nm, wherein said surface stabilizer is not copolymers of vinyl pyrrolidone and vinyl acetate.

27. (Original) The method of claim 26, wherein the nanoparticulate α -integrin antagonist is an $\alpha_4\beta_1$ -integrin antagonist.

28. (Original) The method of claim 27, wherein the $\alpha_4\beta_1$ -integrin antagonist is ELND001.

29. (Original) The method of claim 26 wherein the contacting comprises grinding, wet grinding, homogenizing, precipitation, supercritical fluid particle generation techniques, or emulsion techniques.

30. (Previously Presented) The method of claim 26, wherein the effective average particle size of the nanoparticulate α -integrin antagonist particles is selected from the group consisting of less than 1900 nm, less than 1800 nm, less than 1700 nm, less than 1600 nm, less than 1500 nm, less than 1400 nm, less than 1300 nm, less than 1200 nm, less than 1100 nm, less than 1000 nm, less than 900 nm, less than 800 nm, less than 700 nm, less than 600 nm, less than

500 nm, less than 400 nm, less than 300 nm, less than 250 nm, less than 200 nm, less than 150 nm, less than 100 nm, less than 75 nm, and less than 50 nm.

31. (Previously Presented) A method of treating a subject in need with a nanoparticulate integrin antagonist formulation comprising administering to the subject an effective amount of a nanoparticulate composition comprising:

(a) particles of at least one α -integrin antagonist or a salt thereof having an effective average particle size of less than 2000 nm; and

(b) at least one surface stabilizer,

wherein said surface stabilizer is not copolymers of vinyl pyrrolidone and vinyl acetate.

32. (Original) The method of claim 31, wherein the nanoparticulate α -integrin antagonist is an $\alpha_4\beta_1$ -integrin antagonist.

33. (Original) The method of claim 32, wherein the $\alpha_4\beta_1$ -integrin antagonist is ELND001.

34. (Previously Presented) The method of claim 31, wherein the effective average particle size of the nanoparticulate α -integrin antagonist particles is selected from the group consisting of less than 1900 nm, less than 1800 nm, less than 1700 nm, less than 1600 nm, less than 1500 nm, less than 1400 nm, less than 1300 nm, less than 1200 nm, less than 1100 nm, less than 1000 nm, less than 900 nm, less than 800 nm, less than 700 nm, less than 600 nm, less than 500 nm, less than 400 nm, less than 300 nm, less than 250 nm, less than 200 nm, less than 150 nm, less than 100 nm, less than 75 nm, and less than 50 nm.

35. (Original) The method of claim 31 wherein the subject in need is suffering from an inflammatory disease.

36. (Previously Presented) The composition of claim 1, wherein the composition is formulated into a dosage form selected from the group consisting of liquid dispersions, gels, aerosols, ointments, creams, tablets, and capsules.

37. (Previously Presented) The composition of claim 1, wherein the composition is formulated into a dosage form selected from the group consisting of lyophilized formulations, fast melt formulations, controlled release formulations, delayed release formulations, extended release formulations, pulsatile release formulations, and mixed immediate release and controlled release formulations.

The Listing of Claims will replace all prior versions, and listings, of claims in the application.

LISTING OF CLAIMS

1. (Currently Amended) A composition comprising:
 - (a) at least one stable leukotriene receptor antagonist having an effective average particle size of less than about 2000 nm;
 - (b) at least one surface stabilizer; and
 - (c) at least one corticosteroid.
2. (Original) The composition of claim 1 wherein the leukotriene receptor antagonist is selected from the group consisting of montelukast, zafirlukast, zileuton, pranlukast, leucettamine A and related imidazole alkaloids from the marine sponge *Leucetta microraphis*, ONO-4057, and LY293111, their salts, prodrugs, esters and combinations thereof.
3. (Original) The composition of claim 2 wherein the corticosteroid is selected from the group consisting of fluticasone, fluticasone propionate, budesonide, triamcinolone, triamcinolone acetonide, mometasone, flunisolide, flunisolide hemihydrate, dexamethasone, triamincinolone, beclomethasone, beclomethasone dipropionate, fluocinolone, fluocinonide, betamethasone, mometasone, mometasone furoate monohydrate, cortisone, hydrocortisone, methylprednisolone, prednisolone, prednisone, and combinations thereof.
4. (Original) The composition of claim 1, wherein the corticosteroid has an effective average particle size of less than about 2000 nm, and the corticosteroid is present in combination with particle size of less than about 2000 nm, and the corticosteroid is present in combination with at least one surface stabilizer, wherein the corticosteroid surface stabilizer can be the same as or different from the leukotriene receptor antagonist surface stabilizer of claim 1.
5. (Original) The composition of claim 4, wherein the corticosteroid particles have a size selected from the group consisting of less than about 1900 nm, less than about 1800 nm,

less than about 1700 nm, less than about 1600 nm, less than about 1500 nm, less than about 1400 nm, less than about 1300 nm, less than about 1200 nm, less than about 1100 nm, less than about 1000 nm, less than about 900 nm, less than about 800 nm, less than about 700 nm, less than about 650 nm, less than about 600 nm, less than about 550 nm, less than about 500 nm, less than about 450 nm, less than about 400 nm, less than about 350 nm, less than about 300 nm, less than about 250 nm, less than about 200 nm, less than about 150 nm, less than about 100 nm, less than about 75 nm, or less than about 50 nm.

6. (Original) The composition of claim 1, wherein the leukotriene receptor antagonist particles have a size selected from the group consisting of less than about 1900 nm, less than about 1800 nm, less than about 1700 nm, less than about 1600 nm, less than about 1500 nm, less than about 1400 nm, less than about 1300 nm, less than about 1200 nm, less than about 1100 nm, less than about 1000 nm, less than about 900 nm, less than about 800 nm, less than about 700 nm, less than about 650 nm, less than about 600 nm, less than about 550 nm, less than about 500 nm, less than about 450 nm, less than about 400 nm, less than about 350 nm, less than about 300 nm, less than about 250 nm, less than about 200 nm, less than about 150 nm, less than about 100 nm, less than about 75 nm, or less than about 50 nm.

7. (Original) The composition of claim 1 comprising a leukotriene receptor antagonist at a concentration selected from the group consisting of about 10 mg/mL or more, about 100 mg/mL or more, about 200 mg/mL or more, about 400 mg/mL or more, and about 600 mg/mL.

8. (Original) The composition of claim 1 comprising a corticosteroid at a concentration selected from the group consisting of about 10 mg/mL or more, about 100 mg/mL or more, about 200 mg/mL or more, about 400 mg/mL or more, and about 600 mg/mL.

9. (Original) The composition of claim 1, wherein the composition is formulated into an aerosol and:

- (a) the amount of leukotriene receptor antagonist is from about 0.1 to about 10% by weight;
- (b) the amount of the corticosteroid can range from about 0.01 to about 10% by weight; or
- (c) a combination of (a) and (b).

10. (Original) The composition of claim 1 formulated into an aerosol dosage form, wherein the aerosol is formed from a liquid dispersion of droplets comprising the composition of claim 1 and the droplets have a mass median aerodynamic diameter selected from the group consisting of less than or equal to 100 microns, and about 30 to about 60 microns, about 0.1 to about 10 microns, about 2 to about 6 microns, and less than about 2 microns.

11. (Original) The aerosol composition of claim 10, wherein substantially all of the liquid dispersion droplets of the aerosol comprise at least one nanoparticulate leukotriene receptor antagonist particle, at least one corticosteroid particle, or at least one leukotriene receptor antagonist particle and at least one corticosteroid particle.

12. (Original) The composition of claim 1 formulated into an aqueous aerosol, wherein the leukotriene receptor antagonist is present at about 0.05 mg/mL up to about 600 mg/mL and the corticosteroid is present at about 0.05 mg/mL up to about 600 mg/mL.

13. (Original) The composition of claim 1 formulated into an aerosol dosage form, wherein the aerosol is formed from a dry powder of aggregates of the composition of claim 1, wherein the aggregates have a mass median aerodynamic diameter selected from the group consisting of less than or equal to 100 microns, about 30 to about 60 microns, about 0.1 to about 10 microns, about 2 to about 6 microns, and less than about 2 microns.

14. (Original) The composition of claim 1 formulated into a dry powder, wherein the leukotriene receptor antagonist is present at about 0.05 mg/g to about 990 mg/g and the corticosteroid is present at about 0.05 mg/g to about 990 mg/g.

15. (Original) The composition of claim 13, wherein substantially all of the aggregates of dry powder comprise at least one nanoparticulate leukotriene receptor antagonist particle, at least one corticosteroid particle, or at least one leukotriene receptor antagonist particle and at least one corticosteroid particle.
16. (Original) The composition of claim 1 formulated into an aerosol dosage form, wherein the composition is suitable for aerosol administration of the leukotriene receptor antagonist and corticosteroid dosage in about 15 seconds or less.
17. (Original) The composition of claim 1 formulated into an aerosol dosage form and further comprising a propellant that is administered from a multi-dose inhaler.
18. (Original) The composition of claim 1, wherein the composition is formulated for administration selected from the group consisting of oral, pulmonary, otic, rectal, ocular, ophthalmic, colonic, parenteral, intracisternal, intravaginal, intravenous, intraperitoneal, local, buccal, nasal, and topical administration.
19. (Original) The composition of claim 1, wherein the composition further comprises one or more pharmaceutically acceptable excipients, carriers, or a combination thereof.
20. (Original) The composition of claim 1, wherein the surface stabilizer is selected from the group consisting of a non-ionic surface stabilizer, an anionic surface stabilizer, a cationic surface stabilizer, a zwitterionic surface stabilizer, and an ionic surface stabilizer.
21. (Original) The composition of claim 1, wherein the at least one surface stabilizer is selected from the group consisting of cetyl pyridinium chloride, gelatin, casein, phosphatides, dextran, glycerol, gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glycerol monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers, polyoxyethylene

castor oil derivatives, polyoxyethylene sorbitan fatty acid esters, polyethylene glycols, dodecyl trimethyl ammonium bromide, polyoxyethylene stearates, colloidal silicon dioxide, phosphates, sodium dodecylsulfate, carboxymethylcellulose calcium, hydroxypropyl celluloses, hypromellose, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hypromellose phthalate, noncrystalline cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol, polyvinylpyrrolidone, 4-(1, 1, 3, 3-tetramethylbutyl)-phenol polymer with ethylene oxide and formaldehyde, polyxamers; poloxamines, a charged phospholipid, dioctylsulfosuccinate, dialkylesters of sodium sulfosuccinic acid, sodium lauryl sulfate, alkyl aryl polyether sulfonates, mixtures of sucrose stearate and sucrose distearate, p-isononylphenoxypoly-(glycidol), decanoyl-N-methylglucamide; n-decyl beta-D-glucopyranoside; n-decyl beta-D-maltopyranoside; n-dodecyl beta-D-glucopyranoside; n-dodecyl beta-D-maltoside; heptanoyl-N-methylglucamide; n-heptyl- beta-D-glucopyranoside; n-heptyl beta-D-thiogluconoside; n-hexyl beta-D-glucopyranoside; nonanoyl-N-methylglucamide; n-nonyl beta-D-glucopyranoside; octanoyl-N-methylglucamide; n-octyl-beta-D-glucopyranoside; octyl beta-D-thiogluconoside; lysozyme, PEG-phospholipid, PEG-cholesterol, PEG-cholesterol derivative, PEG-vitamin A, PEG-vitamin E, random copolymers of vinyl acetate and vinyl pyrrolidone, cationic polymers, cationic biopolymers, cationic polysaccharides, cationic celluloses, cationic alginate, cationic non-polymeric compounds, cationic phospholipids, cationic lipids, polymethylmethacrylate trimethylammonium bromide, sulfonium compounds, polyvinylpyrrolidone-2-dimethylaminoethyl methacrylate dimethyl sulfate, hexadecyltrimethyl ammonium bromide, phosphonium compounds, quarternary ammonium compounds, benzyl-di(2-chloroethyl)ethylammonium bromide, coconut trimethyl ammonium chloride, coconut trimethyl ammonium bromide, coconut methyl dihydroxyethyl ammonium chloride, coconut methyl dihydroxyethyl ammonium bromide, decyl triethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium bromide, C₁₂₋₁₅dimethyl hydroxyethyl ammonium chloride, C₁₂₋₁₅dimethyl hydroxyethyl ammonium chloride bromide, coconut dimethyl hydroxyethyl ammonium chloride, coconut dimethyl hydroxyethyl ammonium bromide, myristyl trimethyl ammonium methyl sulphate, lauryl dimethyl benzyl ammonium chloride, lauryl dimethyl benzyl ammonium bromide, lauryl dimethyl (ethenoxy)₄ ammonium chloride, lauryl dimethyl

(ethenoxy)₄ ammonium bromide, N-alkyl (C₁₂₋₁₈)dimethylbenzyl ammonium chloride, N-alkyl (C₁₄₋₁₈)dimethyl-benzyl ammonium chloride, N-tetradecyldimethylbenzyl ammonium chloride monohydrate, dimethyl didecyl ammonium chloride, N-alkyl and (C₁₂₋₁₄) dimethyl 1-naphthylmethyl ammonium chloride, trimethylammonium halide, alkyl-trimethylammonium salts, dialkyl-dimethylammonium salts, lauryl trimethyl ammonium chloride, ethoxylated alkyamidoalkyldialkylammonium salt, an ethoxylated trialkyl ammonium salt, dialkylbenzene dialkylammonium chloride, N-didecyldimethyl ammonium chloride, N-tetradecyldimethylbenzyl ammonium, chloride monohydrate, N-alkyl(C₁₂₋₁₄) dimethyl 1-naphthylmethyl ammonium chloride, dodecyldimethylbenzyl ammonium chloride, dialkyl benzenealkyl ammonium chloride, lauryl trimethyl ammonium chloride, alkylbenzyl methyl ammonium chloride, alkyl benzyl dimethyl ammonium bromide, C₁₂ trimethyl ammonium bromides, C₁₅ trimethyl ammonium bromides, C₁₇ trimethyl ammonium bromides, dodecylbenzyl triethyl ammonium chloride, poly-diallyldimethylammonium chloride, dimethyl ammonium chlorides, alkyldimethylammonium halogenides, tricetyl methyl ammonium chloride, decyltrimethylammonium bromide, dodecyltriethylammonium bromide, tetradecyltrimethylammonium bromide, methyl trioctylammonium chloride, tetrabutylammonium bromide, benzyl trimethylammonium bromide, chloride, choline esters, benzalkonium chloride, stearalkonium chloride compounds, cetyl pyridinium bromide, cetyl pyridinium chloride, halide salts of quaternized polyoxyethylalkylamines, alkyl pyridinium salts; amines, amine salts, amine oxides, imide azolinium salts, protonated quaternary acrylamides, methylated quaternary polymers, and cationic guar.

22. (Withdrawn) A method of making a nano-particulate leukotriene receptor antagonist and corticosteroid composition comprising:

- (a) contacting particles of at least one leukotriene receptor antagonist with at least one surface stabilizer for a time and under conditions sufficient to provide a nanoparticulate leukotriene receptor antagonist composition having an effective average particle size of less than about 2,000 nm; and
- (b) adding a corticosteroid to the composition.

23. (Withdrawn) The method of claim 22, further comprising contacting particles of the corticosteroid with at least one surface stabilizer for a time and under conditions sufficient to provide a nanoparticulate corticosteroid composition having an effective average particle size of less than about 2,000 nm.
24. (Withdrawn) The method of claim 22, wherein the contacting comprising grinding, homogenization, precipitation, or super critical fluids processing.
25. (Withdrawn) A method of administering to a patient in need a leukotriene receptor antagonist and corticosteroid composition comprising:
- (a) at least one leukotriene receptor antagonist having an effective average particle size of less than about 2000 nm;
 - (b) at least one surface stabilizer; and
 - (c) at least one corticosteroid.
26. (Withdrawn) The method of claim 25, wherein the composition is an aerosol of an aqueous dispersion of a nanoparticulate leukotriene receptor antagonist and a nanoparticulate corticosteroid, wherein essentially each droplet of the aerosol comprises at least one nanoparticulate leukotriene receptor antagonist particle, at least one nanoparticulate corticosteroid particle, or at least one leukotriene receptor antagonist particle and at least one nanoparticulate corticosteroid particle.
27. (Withdrawn) The method of claim 26, wherein the leukotriene receptor antagonist is selected from the group consisting of montelukast, zafirlukast, zileuton, pranlukast, leucettamine A and related imidazole alkaloids from the marine sponge *Leucetta microaphis*, ONO-4057, and LY293111, their salts, prodrugs, esters and combinations thereof.
28. (Withdrawn) The method of claim 26, wherein the corticosteroid is selected from the group consisting of fluticasone, gluticasone propionate, budesonide, triamcinolone, triamcinolone acetonide, mometasone, flunisolide, flunisolide hemihydrate, dexamethasone, triamincinolone, beclomethasone, beclomethasone dipropionate, fluocinolone, fluocinonide,

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betamethasone, mometasone, mometasone furonate monohydrate, cortisone, hydrocortisone, methylprednisolone, prednisolone, prednisone, and combinations thereof.

AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions of claims in the application.

1. (Original) A nanoparticulate mitogen-activated protein (MAP) kinase inhibitor composition comprising:
 - (a) particles of a poorly soluble MAP kinase inhibitor or a salt thereof having an effective average particle size of less than about 2000 nm; and
 - (b) associated with the surface thereof at least one surface stabilizer.
2. (Original) The composition of claim 1, wherein the at least one MAP kinase inhibitor is selected from the group consisting of PD 184352, VX-745, SB 202190, Anisomycin, PD 98059, SB 203580, U0126, AG 126, Apigenin, HSP25 Kinase Inhibitor, 5-Iodotubercidin, MAP Kinase Antisense Oligonucleotide, Control MAP Kinase Oligonucleotide, MAP Kinase Cascade Inhibitor, MAP Kinase Inhibitor Set 1, MAP Kinase Inhibitor Set 2, MEK Inhibitor Set, Olomoucine, Iso Olomoucine, N⁹ Isopropyl Olomoucine, p38 MAP Kinase Inhibitor, PD 169316, SB 202474, SB 202190 Hydrochloride, SB 202474 Dihydrochloride, SB 203580 Sulfone, Ioto-SB 203580, SB 220025, SC 68376, SKF-86002, Tyrphostin AG 126, U0124, U0125, and ZM 336372.
3. (Cancelled)
4. (Original) The composition of claim 1, wherein the MAP kinase inhibitor is selected from the group consisting of a crystalline phase, an amorphous phase, a semi-crystalline phase, a semi-amorphous phase, and mixtures thereof.
5. (Original) The composition of claim 1, wherein the effective average particle size of the nanoparticulate MAP kinase inhibitor is selected from the group consisting of less than about 1900 nm, less than about 1800 nm, less than about 1700 nm, less than about 1600 nm, less

than about 1500 nm, less than about 1400 nm, less than about 1300 nm, less than about 1200 nm, less than about 1100 nm, less than about 1000 nm, less than about 900 nm, less than about 800 nm, less than about 700 nm, less than about 600 nm, less than about 500 nm, less than about 400 nm, less than about 300 nm, less than about 250 nm, less than about 200 nm, less than about 100 nm, less than about 75 nm, and less than about 50 nm.

6. (Previously Presented) The composition of claim 1, wherein the composition is formulated:

(a) for administration selected from the group consisting of oral, pulmonary, rectal, ophthalmic, colonic, parenteral, intracisternal, intravaginal, intraperitoneal, local, buccal, nasal, and topical administration;

(b) into a dosage form selected from the group consisting of liquid dispersions, gels, aerosols, ointments, creams, controlled release formulations, fast melt formulations, lyophilized formulations, tablets, capsules, delayed release formulations, extended release formulations, pulsatile release formulations, and mixed immediate release and controlled release formulations; or

(c) a combination of (a) and (b).

7. (Cancelled)

8. (Original) The composition of claim 1, wherein the composition further comprises one or more pharmaceutically acceptable excipients, carriers, or a combination thereof.

9. (Previously Presented) The composition of claim 1, wherein:

(a) the MAP kinase inhibitor is present in an amount selected from the group consisting of from about 99.5% to about 0.001%, from about 95% to about 0.1%, and from about

90% to about 0.5%, by weight, based on the total combined weight of the MAP kinase inhibitor and at least one surface stabilizer, not including other excipients;

(b) the at least one surface stabilizer is present in an amount selected from the group consisting of from about 0.5% to about 99.999%, from about 5.0% to about 99.9%, and from about 10% to about 99.5%, by weight, based on the total combined weight of the at least one MAP kinase inhibitor and at least one surface stabilizer, not including other excipients; or

(c) a combination of (a) and (b).

10. (Cancelled)

11. (Original) The composition of claim 1, comprising at least two surface stabilizers.

12. (Original) The composition of claim 1, wherein the surface stabilizer is selected from the group consisting of an anionic surface stabilizer, a cationic surface stabilizer, an ionic surface stabilizer, and a zwitterionic surface stabilizer.

13. (Currently Amended) The composition of claim 12, wherein at least one surface stabilizer is selected from the group consisting of cetyl pyridinium chloride, gelatin, casein, phosphatides, dextran, glycerol, gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glycerol monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers, polyoxyethylene castor oil derivatives oils, polyoxyethylene sorbitan fatty acid esters, polyethylene glycols, dodecyl trimethyl ammonium bromide, polyoxyethylene stearates, colloidal silicon dioxide, phosphates, sodium dodecylsulfate, carboxymethylcellulose calcium, hydroxypropyl celluloses, hydroxypropyl methylcellulose, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hydroxypropylmethylcellulose phthalate, noncrystalline cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol, polyvinylpyrrolidone, 4-(1,1,3,3-tetramethylbutyl)-phenol polymer with

ethylene oxide and formaldehyde, poloxamers; poloxamines, a charged phospholipid, dioctylsulfosuccinate, dialkylesters of sodium sulfosuccinic acid, sodium lauryl sulfate, alkyl aryl polyether sulfonates, mixtures of sucrose stearate and sucrose distearate, $C_{18}H_{37}CH_2C(O)N(CH_3)-CH_2(CHOH)_4(CH_2OH)_2$, p-isononylphenoxypoly-(glycidol), decanoyl-N-methylglucamide; n-decyl β -D-glucopyranoside; n-decyl β -D-maltopyranoside; n-dodecyl β -D-glucopyranoside; n-dodecyl β -D-maltoside; heptanoyl-N-methylglucamide; n-heptyl- β -D-glucopyranoside; n-heptyl β -D-thioglucoside; n-hexyl β -D-glucopyranoside; nonanoyl-N-methylglucamide; n-nonyl β -D-glucopyranoside; octanoyl-N-methylglucamide; n-octyl- β -D-glucopyranoside; octyl β -D-thioglucopyranoside; lysozyme, PEG-phospholipid, PEG-cholesterol, ~~PEG-cholesterol derivative~~, PEG-vitamin A, PEG-vitamin E, random copolymers of vinyl acetate and vinyl pyrrolidone, cationic lipids, polymethylmethacrylate trimethylammonium bromide, sulfonium compounds, polyvinylpyrrolidone-2-dimethylaminoethyl methacrylate dimethyl sulfate, hexadecyltrimethyl ammonium bromide, phosphonium compounds, quarternary ammonium compounds, benzyl-di(2-chloroethyl)ethylammonium bromide, coconut trimethyl ammonium chloride, coconut trimethyl ammonium bromide, coconut methyl dihydroxyethyl ammonium chloride, coconut methyl dihydroxyethyl ammonium bromide, decyl triethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride bromide, C_{12-15} dimethyl hydroxyethyl ammonium chloride, C_{12-15} dimethyl hydroxyethyl ammonium chloride bromide, coconut dimethyl hydroxyethyl ammonium chloride, coconut dimethyl hydroxyethyl ammonium bromide, myristyl trimethyl ammonium methyl sulphate, lauryl dimethyl benzyl ammonium chloride, lauryl dimethyl benzyl ammonium bromide, lauryl dimethyl (ethenoxy)₄ ammonium chloride, lauryl dimethyl (ethenoxy)₄ ammonium bromide, N-alkyl (C_{12-18})dimethylbenzyl ammonium chloride, N-alkyl (C_{14-18})dimethyl-benzyl ammonium chloride, N-tetradecylidmethylbenzyl ammonium chloride monohydrate, dimethyl didecyl ammonium chloride, N-alkyl and (C_{12-14}) dimethyl 1-naphthylmethyl ammonium chloride, trimethylammonium halide, alkyl-trimethylammonium salts, dialkyl-dimethylammonium salts, lauryl trimethyl ammonium chloride, ethoxylated

alkyamidoalkyldialkylammonium salt, an ethoxylated trialkyl ammonium salt, dialkylbenzene dialkylammonium chloride, N-didecyldimethyl ammonium chloride, N-tetradecyldimethylbenzyl ammonium, chloride monohydrate, N-alkyl(C₁₂₋₁₄) dimethyl 1-naphthylmethyl ammonium chloride, dodecyldimethylbenzyl ammonium chloride, dialkyl benzenealkyl ammonium chloride, lauryl trimethyl ammonium chloride, alkylbenzyl methyl ammonium chloride, alkyl benzyl dimethyl ammonium bromide, C₁₂ trimethyl ammonium bromides, C₁₅ trimethyl ammonium bromides, C₁₇ trimethyl ammonium bromides, dodecylbenzyl triethyl ammonium chloride, polydiallyldimethylammonium chloride (DADMAC), dimethyl ammonium chlorides, alkyldimethylammonium halogenides, tricetyl methyl ammonium chloride, decyltrimethylammonium bromide, dodecyltriethylammonium bromide, tetradecyltrimethylammonium bromide, methyl trioctylammonium chloride, ~~POLYQUAT 10™~~ polyquaternium 10, tetrabutylammonium bromide, benzyl trimethylammonium bromide, choline esters, benzalkonium chloride, stearalkonium chloride compounds, cetyl pyridinium bromide, cetyl pyridinium chloride, halide salts of quaternized polyoxyethylalkylamines, ~~MIRAPOL™~~, ~~ALKAQUAT™~~ quaternized ammonium salt polymers, alkyl pyridinium salts; amines, amine salts, amine oxides, imide azolinium salts, protonated quaternary acrylamides, methylated quaternary polymers, and cationic guar.

14. (Cancelled)

15. (Previously Presented) The composition of claim 13, wherein the composition is bioadhesive.

16. (Original) The composition of claim 1, wherein the composition comprises more than one MAP kinase inhibitor.

17. (Original) The composition of claim 16, wherein at least one MAP kinase inhibitor has an effective average particle size which is greater than about 2 microns.

18. (Original) The composition of claim 1, additionally comprising at least one nanoparticulate MAP kinase inhibitor composition having an effective average particle size of less than about 2 microns, wherein said additional nanoparticulate MAP kinase inhibitor composition has an effective average particle size which is different than the particle size of the nanoparticulate MAP kinase inhibitor composition of claim 1.

19. (Original) The composition of claim 1, additionally comprising at least one non-MAP kinase inhibitor active agent.

20. (Original) The composition of claim 19, wherein said active agent is selected from the group consisting of amino acids, proteins, peptides, nucleotides, anti-obesity drugs, nutraceuticals, dietary supplements, central nervous symptom stimulants, carotenoids, corticosteroids, elastase inhibitors, anti-fungals, alkylxanthine, oncology therapies, anti-emetics, analgesics, opioids, antipyretics, cardiovascular agents, anti-inflammatory agents, anthelmintics, anti-arrhythmic agents, antibiotics, anticoagulants, antidepressants, antidiabetic agents, antiepileptics, antihistamines, antihypertensive agents, antimuscarinic agents, antimycobacterial agents, antineoplastic agents, immunosuppressants, antithyroid agents, antiviral agents, anxiolytics, sedatives, astringents, alpha-adrenergic receptor blocking agents, beta-adrenoceptor blocking agents, blood products, blood substitutes, cardiac inotropic agents, contrast media, corticosteroids, cough suppressants, diagnostic agents, diagnostic imaging agents, diuretics, dopaminergics, haemostatics, immunological agents, lipid regulating agents, muscle relaxants, parasympathomimetics, parathyroid calcitonin and biphosphonates, prostaglandins, radio-pharmaceuticals, sex hormones, anti-allergic agents, stimulants, anoretics, sympathomimetics, thyroid agents, vasodilators, vasomodulator, xanthines, Mu receptor antagonists, Kappa receptor antagonists, non-narcotic analgesics, monoamine uptake inhibitors, adenosine regulating agents,

cannabinoid derivatives, Substance P antagonists, neurokinin-1 receptor antagonists, and sodium channel blockers.

21. (Original) The composition of claim 20, wherein said nutraceutical is selected from the group consisting of lutein, folic acid, fatty acids, fruit extracts, vegetable extracts, vitamin supplements, mineral supplements, phosphatidylserine, lipoic acid, melatonin, glucosamine/chondroitin, Aloe Vera, Guggul, glutamine, amino acids, green tea, lycopene, whole foods, food additives, herbs, phytonutrients, antioxidants, flavonoid constituents of fruits, evening primrose oil, flax seeds, fish oils, marine animal oils, and probiotics.

22. (Previously Presented) The composition of claim 19, wherein:

(a) at least one non-MAP kinase inhibitor active agent has an effective average particle size of less than about 2 microns; or

(b) at least one non-MAP kinase inhibitor active agent has an effective average particle size of greater than about 2 microns.

23. (Cancelled)

24. (Original) The composition of claim 1, wherein upon administration the composition redisperses such that the MAP kinase inhibitor particles have a particle size selected from the group consisting of less than about 2 microns, less than about 1900 nm, less than about 1800 nm, less than about 1700 nm, less than about 1600 nm, less than about 1500 nm, less than about 1400 nm, less than about 1300 nm, less than about 1200 nm, less than about 1100 nm, less than about 1000 nm, less than about 900 nm, less than about 800 nm, less than about 700 nm, less than about 600 nm, less than about 500 nm, less than about 400 nm, less than about 300 nm, less than about 250 nm, less than about 200 nm, less than about 150 nm, less than about 100 nm, less than about 75 nm, and less than about 50 nm.

25. (Original) The composition of claim 24, wherein the composition is a solid dosage form.

26. (Original) The composition of claim 1, wherein the composition has been sterile filtered.

27. (Previously Presented) The composition of claim 1, wherein:

(a) the composition does not produce significantly different absorption levels when administered under fed as compared to fasting conditions;

(b) the composition does not produce significantly different rates of absorption (T_{\max}) when administered under fed as compared to fasting conditions; or

(c) a combination of (a) and (b).

28. (Previously Presented) The composition of claim 1, wherein:

(a) the difference in absorption of the nanoparticulate MAP kinase inhibitor composition of the invention, when administered in the fed versus the fasted state, is selected from the group consisting of less than about 100%, less than about 90%, less than about 80%, less than about 70%, less than about 60%, less than about 50%, less than about 40%, less than about 35%, less than about 30%, less than about 25%, less than about 20%, less than about 15%, less than about 10%, less than about 5%, and less than about 3%; or

(b) the difference in the T_{\max} for the nanoparticulate MAP kinase inhibitor composition of the invention, when administered in the fed versus the fasted state, is less than about 100%, less than about 90%, less than about 80%, less than about 70%, less than about 60%, less than about 50%, less than about 40%, less than about 30%, less than about 20%, less than about 15%, less than about 10%, less than about 5%, and less than about 3%; or

(c) a combination of (a) and (b).

29.-30. (Cancelled)

31. (Previously Presented) The composition of claim 1, wherein:

- (a) upon administration the T_{\max} is less than that of a conventional non-nanoparticulate composition of the same MAP kinase inhibitor, administered at the same dosage;
- (b) upon administration the C_{\max} of the composition is greater than the C_{\max} of a conventional non-nanoparticulate composition of the same MAP kinase inhibitor, administered at the same dosage; or
- (c) a combination of (a) and (b).

32. (Original) The composition of claim 1, wherein in comparative pharmacokinetic testing with a non-nanoparticulate composition of the same MAP kinase inhibitor, administered at the same dosage, the nanoparticulate composition exhibits a T_{\max} selected from the group consisting of less than about 100%, less than about 90%, less than about 80%, less than about 70%, less than about 60%, less than about 50%, less than about 40%, less than about 30%, less than about 25%, less than about 20%, less than about 15%, and less than about 10% of the T_{\max} exhibited by the non-nanoparticulate composition of the MAP kinase inhibitor.

33. (Original) The composition of claim 1, wherein following administration the composition has a T_{\max} selected from the group consisting of less than about 2.5 hours, less than about 2.25 hours, less than about 2 hours, less than about 1.75 hours, less than about 1.5 hours, less than about 1.25 hours, less than about 1.0 hours, less than about 50 minutes, less than about 40 minutes, less than about 30 minutes, less than about 25 minutes, less than about 20 minutes, less than about 15 minutes, and less than about 10 minutes.

34. (Cancelled)

35. (Original) The composition of claim 1, wherein in comparative pharmacokinetic testing with a non-nanoparticulate composition of the same MAP kinase inhibitor, administered at the same dosage, the nanoparticulate composition exhibits a C_{max} selected from the group consisting of greater than about 5%, greater than about 10%, greater than about 15%, greater than about 20%, greater than about 30%, greater than about 40%, greater than about 50%, greater than about 60%, greater than about 70%, greater than about 80%, greater than about 90%, greater than about 100%, greater than about 110%, greater than about 120%, greater than about 130%, greater than about 140%, and greater than about 150% than the C_{max} exhibited by the non-nanoparticulate composition of the MAP kinase inhibitor.

36. (Original) A method of making a mitogen-activated protein (MAP) kinase inhibitor composition comprising contacting particles of at least one poorly soluble MAP kinase inhibitor with at least one surface stabilizer for a time and under conditions sufficient to provide a MAP kinase inhibitor composition having an effective average particle size of less than about 2 microns.

37.-55. (Cancelled)

56. (Withdrawn) A method of treating a subject in need with a mitogen-activated protein (MAP) kinase inhibitor composition comprising administering to the subject an effective amount of a MAP kinase inhibitor composition comprising:

- (a) particles of a poorly soluble MAP kinase inhibitor or a salt thereof having an effective average particle size of less than about 2000 nm; and
- (b) associated with the surface thereof at least one surface stabilizer.

57. (Withdrawn) The method of claim 56, wherein the at least one MAP kinase inhibitor is selected from the group consisting of PD 184352, VX-745, SB 202190, Anisomycin, PD 98059, SB 203580, U0126, AG 126, Apigenin, HSP25 Kinase Inhibitor, 5-Iodotubercidin, MAP Kinase Antisense Oligonucleotide, Control MAP Kinase Oligonucleotide, MAP Kinase

Cascade Inhibitor, MAP Kinase Inhibitor Set 1, MAP Kinase Inhibitor Set 2, MEK Inhibitor Set, Olomoucine, Iso Olomoucine, N⁹ Isopropyl Olomoucine, p38 MAP Kinase Inhibitor, PD 169316, SB 202474, SB 202190 Hydrochloride, SB 202474 Dihydrochloride, SB 203580 Sulfone, Ioto-SB 203580, SB 220025, SC 68376, SKF-86002, Tyrphostin AG 126, U0124, U0125, and ZM 336372.

58. (Cancelled)

59. (Withdrawn) The method of claim 56, wherein the effective average particle size of the nanoparticulate MAP kinase inhibitor particles is selected from the group consisting of less than about 1900 nm, less than about 1800 nm, less than about 1700 nm, less than about 1600 nm, less than about 1500 nm, less than about 1400 nm, less than about 1300 nm, less than about 1200 nm, less than about 1100 nm, less than about 1000 nm, less than about 900 nm, less than about 800 nm, less than about 700 nm, less than about 600 nm, less than about 500 nm, less than about 400 nm, less than about 300 nm, less than about 250 nm, less than about 200 nm, less than about 100 nm, less than about 75 nm, and less than about 50 nm.

60.-83. (Cancelled)

84. (Withdrawn) The method of claim 56, wherein the method is used to treat an condition where a selective MAP kinase inhibitor is indicated.

85. (Withdrawn) The method of claim 56, wherein the method is used to treat an inflammatory disease.

86. (Withdrawn) The method of claim 56, wherein the method is used to treat a condition selected from the group consisting of rheumatoid arthritis and Crohn's disease.

87. (Withdrawn) The method of claim 56, wherein the subject is a human.

LISTING OF CLAIMS

1. (Previously Presented) A composition comprising:
 - (a) particles of metaxalone or a salt thereof, wherein the metaxalone particles have an effective average particle size of less than 2000 nm; and
 - (b) at least one surface stabilizer adsorbed on the surface of the metaxalone particles.
2. (Previously Presented) The composition of claim 1, wherein the metaxalone is selected from the group consisting of a crystalline phase, an amorphous phase, and a semi-crystalline phase.
3. (Previously Presented) The composition of claim 1, wherein the effective average particle size of the metaxalone particles is selected from the group consisting of less than 1900 nm, less than 1800 nm, less than 1700 nm, less than 1600 nm, less than 1500 nm, less than 1400 nm, less than 1300 nm, less than 1200 nm, less than 1100 nm, less than 1000 nm, less than 900 nm, less than 800 nm, less than 700 nm, less than 600 nm, less than 500 nm, less than 400 nm, less than 300 nm, less than 250 nm, less than 200 nm, less than 100 nm, less than 75 nm, and less than 50 nm.
4. (Original) The composition of claim 1, wherein the composition is formulated for administration selected from the group consisting of oral, pulmonary, rectal, ophthalmic, colonic, parenteral, intracisternal, intravaginal, intraperitoneal, local, buccal, nasal, and topical administration.
5. (Original) The composition of claim 1 formulated into a dosage form selected from the group consisting of liquid dispersions, oral suspensions, gels, aerosols, ointments, creams, controlled release formulations, fast melt formulations, lyophilized formulations, tablets, capsules, delayed release formulations, extended release formulations, pulsatile release formulations, and mixed immediate release and controlled release formulations.

6. (Original) The composition of claim 1, wherein the composition further comprises one or more pharmaceutically acceptable excipients, carriers, or a combination thereof.

7. (Original) The composition of claim 1, wherein:

(a) the metaxalone or a salt thereof is present in an amount selected from the group consisting of from about 99.5% to about 0.001%, from about 95% to about 0.1%, and from about 90% to about 0.5%, by weight, based on the total combined weight of the metaxalone or a salt thereof and at least one surface stabilizer, not including other excipients; and

(b) the at least one surface stabilizer is present in an amount selected from the group consisting of from about 0.5% to about 99.999% by weight, from about 5.0% to about 99.9% by weight, and from about 10% to about 99.5% by weight, based on the total combined dry weight of the metaxalone or a salt thereof and at least one surface stabilizer, not including other excipients.

8. (Cancelled)

9. (Previously Presented) The composition of claim 1, wherein the at least one surface stabilizer is selected from the group consisting of cetyl pyridinium chloride, gelatin, casein, phosphatides, dextran, glycerol, gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glycerol monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers, polyoxyethylene castor oils, polyoxyethylene sorbitan fatty acid esters, polyethylene glycols, dodecyl trimethyl ammonium bromide, polyoxyethylene stearates, colloidal silicon dioxide, phosphates, sodium dodecylsulfate, carboxymethylcellulose calcium, hydroxypropyl celluloses, hypromellose, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hypromellose phthalate, noncrystalline cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol, polyvinylpyrrolidone, 4-(1,1,3,3-tetramethylbutyl)-phenol polymer with ethylene oxide and formaldehyde, poloxamers; poloxamines, a charged phospholipid, dioctylsulfosuccinate,

dialkylesters of sodium sulfosuccinic acid, sodium lauryl sulfate, alkyl aryl polyether sulfonates, mixtures of sucrose stearate and sucrose distearate, p-isononylphenoxypoly-(glycidol), decanoyl-N-methylglucamide; n-decyl β -D-glucopyranoside; n-decyl β -D-maltopyranoside; n-dodecyl β -D-glucopyranoside; n-dodecyl β -D-maltoside; heptanoyl-N-methylglucamide; n-heptyl- β -D-glucopyranoside; n-heptyl β -D-thioglucoside; n-hexyl β -D-glucopyranoside; nonanoyl-N-methylglucamide; n-nonyl β -D-glucopyranoside; octanoyl-N-methylglucamide; n-octyl- β -D-glucopyranoside; octyl β -D-thioglucopyranoside; lysozyme, PEG-phospholipid, PEG-cholesterols, PEG-vitamin A, random copolymers of vinyl acetate and vinyl pyrrolidone, cationic polymers, cationic biopolymers, cationic polysaccharides, cationic celluloses, cationic alginates, cationic nonpolymeric compounds, cationic phospholipids, cationic lipids, polymethylmethacrylate trimethylammonium bromide, sulfonium compounds, polyvinylpyrrolidone-2-dimethylaminoethyl methacrylate dimethyl sulfate, hexadecyltrimethyl ammonium bromide, phosphonium compounds, quarternary ammonium compounds, benzyl-di(2-chloroethyl)ethylammonium bromide, coconut trimethyl ammonium chloride, coconut trimethyl ammonium bromide, coconut methyl dihydroxyethyl ammonium chloride, coconut methyl dihydroxyethyl ammonium bromide, decyl triethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride bromide, C₁₂₋₁₅dimethyl hydroxyethyl ammonium chloride, C₁₂₋₁₅dimethyl hydroxyethyl ammonium chloride bromide, coconut dimethyl hydroxyethyl ammonium chloride, coconut dimethyl hydroxyethyl ammonium bromide, myristyl trimethyl ammonium methyl sulphate, lauryl dimethyl benzyl ammonium chloride, lauryl dimethyl benzyl ammonium bromide, lauryl dimethyl (ethenoxy)₄ ammonium chloride, lauryl dimethyl (ethenoxy)₄ ammonium bromide, N-alkyl (C₁₂₋₁₈)dimethylbenzyl ammonium chloride, N-alkyl (C₁₄₋₁₈)dimethyl-benzyl ammonium chloride, N-tetradecylidmethylbenzyl ammonium chloride monohydrate, dimethyl didecyl ammonium chloride, N-alkyl and (C₁₂₋₁₄) dimethyl 1-naphthylmethyl ammonium chloride, trimethylammonium halide, alkyl-trimethylammonium salts, dialkyl-dimethylammonium salts, lauryl trimethyl ammonium chloride, ethoxylated alkyamidoalkyldialkylammonium salt, an

ethoxylated trialkyl ammonium salt, dialkylbenzene dialkylammonium chloride, N-didecyldimethyl ammonium chloride, N-tetradecyldimethylbenzyl ammonium, chloride monohydrate, N-alkyl(C₁₂₋₁₄) dimethyl 1-naphthylmethyl ammonium chloride, dodecyldimethylbenzyl ammonium chloride, dialkyl benzenealkyl ammonium chloride, lauryl trimethyl ammonium chloride, alkylbenzyl methyl ammonium chloride, alkyl benzyl dimethyl ammonium bromide, C₁₂ trimethyl ammonium bromides, C₁₅ trimethyl ammonium bromides, C₁₇ trimethyl ammonium bromides, dodecylbenzyl triethyl ammonium chloride, polydiallyldimethylammonium chloride (DADMAC), dimethyl ammonium chlorides, alkyldimethylammonium halogenides, tricetyl methyl ammonium chloride, decyltrimethylammonium bromide, dodecyltriethylammonium bromide, tetradecyltrimethylammonium bromide, methyl trioctylammonium chloride, polyquaternium 10, tetrabutylammonium bromide, benzyl trimethylammonium bromide, choline esters, benzalkonium chloride, stearylalkonium chloride compounds, cetyl pyridinium bromide, cetyl pyridinium chloride, halide salts of quaternized polyoxyethylalkylamines, quaternized ammonium salt polymers, alkyl pyridinium salts; amines, amine salts, amine oxides, imide azolinium salts, protonated quaternary acrylamides, methylated quaternary polymers, and cationic guar.

10. (Previously Presented) The composition of claim 1, wherein the composition is bioadhesive.

11. (Original) The composition of claim 9, wherein the composition is bioadhesive.

12. (Original) The composition of claim 1, comprising at least one primary surface stabilizer and at least one secondary surface stabilizer.

13. (Original) The composition of claim 1, comprising as a surface stabilizer polyvinylpyrrolidone, docusate sodium, lysozyme, or a combination thereof.

14. (Original) The composition of claim 13, comprising as surface stabilizers polyvinylpyrrolidone and docusate sodium.

15. (Previously Presented) The composition of claim 1, further comprising at least one additional metaxalone composition having an effective average particle size which is different than the effective average particle size of the metaxalone composition of claim 1.

16. (Original) The composition of claim 1, additionally comprising one or more non-metaxalone active agents.

17. (Original) The composition of claim 16, wherein said additionally one or more non-metaxalone active agents are selected from the group consisting of amino acids, proteins, peptides, nucleotides, anti-obesity drugs, central nervous system stimulants, carotenoids, corticosteroids, elastase inhibitors, anti-fungals, oncology therapies, anti-emetics, analgesics, cardiovascular agents, anti-inflammatory agents, anthelmintics, anti-arrhythmic agents, antibiotics, anticoagulants, antidepressants, antidiabetic agents, antiepileptics, antihistamines, antihypertensive agents, antimuscarinic agents, antimycobacterial agents, antineoplastic agents, immunosuppressants, antithyroid agents, antiviral agents, anxiolytics, sedatives, astringents, alpha-adrenergic receptor blocking agents, beta-adrenoceptor blocking agents, blood products, blood substitutes, cardiac inotropic agents, contrast media, corticosteroids, cough suppressants, diagnostic agents, diagnostic imaging agents, diuretics, dopaminergics, haemostatics, immunological agents, lipid regulating agents, muscle relaxants, parasympathomimetics, parathyroid calcitonin, parathyroid biphosphonates, prostaglandins, radio-pharmaceuticals, sex hormones, anti-allergic agents, stimulants, anoretics, sympathomimetics, thyroid agents, vasodilators, xanthines, acyclovir, alprazolam, altretamine, amiloride, amiodarone, benztropine mesylate, bupropion, cabergoline, candesartan, cerivastatin, chlorpromazine, ciprofloxacin, cisapride, clarithromycin, clonidine, clopidogrel, cyclobenzaprine, cyproheptadine, delavirdine, desmopressin, diltiazem, dipyridamole, dolasetron, enalapril maleate, enalaprilat, famotidine, felodipine, furazolidone, glipizide, irbesartan, ketoconazole, lansoprazole, loratadine, loxapine,

mebendazole, mercaptopurine, milrinone lactate, minocycline, mitoxantrone, nelfinavir mesylate, nimodipine, norfloxacin, olanzapine, omeprazole, penciclovir, pimozide, tacolimus, quazepam, raloxifene, rifabutin, rifampin, risperidone, rizatriptan, saquinavir, sertraline, sildenafil, acetyl-sulfisoxazole, temazepam, thiabendazole, thioguanine, trandolapril, triamterene, trimetrexate, troglitazone, trovafloxacin, verapamil, vinblastine sulfate, mycophenolate, atovaquone, atovaquone, proguanil, ceftazidime, cefuroxime, etoposide, terbinafine, thalidomide, fluconazole, amsacrine, dacarbazine, teniposide, acetylsalicylate, an NSAID, and a COX-2 inhibitor.

18. (Original) The composition of claim 17, wherein the NSAID is selected from the group consisting of nabumetone, tiaramide, proquazone, bufexamac, flumizole, epirazole, tinoridine, timegadine, dapsone, aspirin, diflunisal, benorylate, fosfosal, diclofenac, alclofenac, fenclofenac, etodolac, indomethacin, sulindac, tolmetin, fentiazac, tilomisole, carprofen, fenbufen, flurbiprofen, ketoprofen, oxaprozin, suprofen, tiaprofenic acid, ibuprofen, naproxen, fenoprofen, indoprofen, pirprofen, flufenamic, mefenamic, meclofenamic, niflumic, oxyphenbutazone, phenylbutazone, apazone, feprazone, piroxicam, sudoxicam, isoxicam, and tenoxicam.

19. (Previously Presented) The composition of claim 17, wherein the COX-2 inhibitor is selected from the group consisting of celecoxib, rofecoxib, meloxicam, valdecoxib, parecoxib, etoricoxib, 4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide, N-(2-cyclohexyloxy-4-nitrophenyl)methanesulfonamide, 5-(4-fluorophenyl)-1-[4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)-1H-pyrazole, 1-fluoro-4-(2-(4-(methylsulfonyl)phenyl)cyclopent-1-enyl)benzene, 4-[5-(4-bromophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]-benzenesulfonamide, 5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-trifluoromethylpyrazole, etodolac, (5,5-dimethyl-3-(3-fluorophenyl)-4-(4-methylsulfonyl)phenyl 2(5H)-furanone), monteleukast, 5-methanesulfonamido-6-(2,4-difluorothiophenyl)-1-indanone, (R)-1-[(4-bromophenyl)methyl]-5-methoxy- β ,2-dimethyl-1H-indole-3-butanoic acid, 1-[(4-bromophenyl)methyl]-5-methoxy- β ,2-dimethyl-1H-indole-3-butanoic acid, 5-methoxy-2-methyl-

1-(2,4,6-trichlorobenzoyl)-1H-indole-3-acetic acid, 5-bromo-2-(4-fluorophenyl)-3-(4-(methylsulfonyl)phenyl)thiophene, 1-(7-tert-butyl-2,3-dihydro-3,3-dimethylbenzo(b)furan-5-yl)-4-cyclopropylbutan-1-one, iguratimod, 4-[[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]methylene]dihydro-2-methyl-2H-1,2-oxazin-3(4H)-one, acetyldiphenylalanyl-leucyl-aspartyl-isoleucyl-isoleucyl-tryptophan, acetyl-(5H-dibenzyl(a,d)cycloheptene-10,11-dihydroglycine-leucyl-aspartyl-isoleucyl-isoleucyl-tryptophan), 5-(3,5-di-tert-butyl-4-hydroxybenzylidene)-2-(methoxyamino)thiazol-4-one, flurbiprofen, nimesulide, nabumetone, flosulide, piroxicam, diclofenac, lumiracoxib, diflumidone, 4-(4-cyclohexyl-2-methyl-5-oxazolyl)-2-fluoro-benzenesulfonamide, 4'-acetyl-2'-(2,4-difluorophenoxy)methanesulfonanilide, N-[5-(4-fluorophenoxy)-2-thienyl]-methanesulfonamide, 5-(4-chlorophenyl)-N-hydroxy-1-(4-methoxyphenyl)-N-methyl-1H-pyrazole-3-propanamide, N-[6-(2,4-difluorophenoxy)-2,3-dihydro-1-oxo-1H-inden-5-yl]-methanesulfonamide, a mixture of 2,6-bis(1,1-dimethylethyl)-4-[(E)-(2-ethyl-1,1-dioxido-5-isothiazolidinylidene)methyl]-phenol and 9,13b-dihydro-1H-dibenz[c,f]imidazo[1,5-a]azepin-3-amine hydrochloride, 6-[[5-(4-chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-yl]methyl]-3(2H)-pyridazinone, 5-(4-chlorobenzoyl)-N-[(4-iodophenyl)sulfonyl]-1,4-dimethyl-1H-pyrrole-2-carboxamide, 7-(3-(4-acetyl-3-methoxy-2-propylphenoxy)propoxy)-3,4-dihydro-8-propyl-2H-1-benzopyran-2-carboxylic acid, pranlukast, and 3-(2-(carboxymethoxy)-4-methoxyphenyl)-1-(3,4-(methylenedioxy)phenyl)-5-(prop-1-yloxy)indan-2-carboxylic acid, heptynysulfide, and 3-(difluoromethyl)-1-(4-methoxyphenyl)-5-[4-(methylsulfinyl)phenyl]-1H-pyrazole.

20. (Previously Presented) The composition of claim 1, wherein upon administration to a mammal the metaxalone particles redisperse such that the particles have an effective average particle size selected from the group consisting of less than 2 microns, less than 1900 nm, less than 1800 nm, less than 1700 nm, less than 1600 nm, less than 1500 nm, less than 1400 nm, less than 1300 nm, less than 1200 nm, less than 1100 nm, less than 1000 nm, less than 900 nm, less than 800 nm, less than 700 nm, less than 600 nm, less than 500 nm, less than 400 nm, less than

300 nm, less than 250 nm, less than 200 nm, less than 150 nm, less than 100 nm, less than 75 nm, and less than 50 nm.

21. (Previously Presented) The composition of claim 1, wherein the composition redisperses in a biorelevant media such that the metaxalone particles have an effective average particle size selected from the group consisting of less than 2 microns, less than 1900 nm, less than 1800 nm, less than 1700 nm, less than 1600 nm, less than 1500 nm, less than 1400 nm, less than 1300 nm, less than 1200 nm, less than 1100 nm, less than 1000 nm, less than 900 nm, less than 800 nm, less than 700 nm, less than 600 nm, less than 500 nm, less than 400 nm, less than 300 nm, less than 250 nm, less than 200 nm, less than 150 nm, less than 100 nm, less than 75 nm, and less than 50 nm.

22. (Original) The composition of claim 21, wherein the biorelevant media is selected from the group consisting of water, aqueous electrolyte solutions, aqueous solutions of a salt, aqueous solutions of an acid, aqueous solutions of a base, and combinations thereof.

23. (Original) The composition of claim 1, wherein the T_{\max} of the metaxalone, when assayed in the plasma of a mammalian subject following administration, is less than the T_{\max} for a non-nanoparticulate metaxalone formulation, administered at the same dosage.

24. (Previously Presented) The composition of claim 23, wherein the T_{\max} is selected from the group consisting of not greater than 90%, not greater than 80%, not greater than 70%, not greater than 60%, not greater than 50%, not greater than 30%, not greater than 25%, not greater than 20%, not greater than 15%, not greater than 10%, and not greater than 5% of the T_{\max} exhibited by a non-nanoparticulate metaxalone formulation, administered at the same dosage.

25. (Original) The composition of claim 1, wherein the C_{\max} of the metaxalone, when assayed in the plasma of a mammalian subject following administration, is greater than the C_{\max} for a non-nanoparticulate metaxalone formulation, administered at the same dosage.

26. (Previously Presented) The composition of claim 25, wherein the C_{\max} is selected from the group consisting of at least 50%, at least 100%, at least 200%, at least 300%, at least 400%, at least 500%, at least 600%, at least 700%, at least 800%, at least 900%, at least 1000%, at least 1100%, at least 1200%, at least 1300%, at least 1400%, at least 1500%, at least 1600%, at least 1700%, at least 1800%, or at least 1900% greater than the C_{\max} exhibited by a non-nanoparticulate formulation of metaxalone, administered at the same dosage.

27. (Original) The composition of claim 1, wherein the AUC of the metaxalone, when assayed in the plasma of a mammalian subject following administration, is greater than the AUC for a non-nanoparticulate metaxalone formulation, administered at the same dosage.

28. (Previously Presented) The composition of claim 27, wherein the AUC is selected from the group consisting of at least 25%, at least 50%, at least 75%, at least 100%, at least 125%, at least 150%, at least 175%, at least 200%, at least 225%, at least 250%, at least 275%, at least 300%, at least 350%, at least 400%, at least 450%, at least 500%, at least 550%, at least 600%, at least 750%, at least 700%, at least 750%, at least 800%, at least 850%, at least 900%, at least 950%, at least 1000%, at least 1050%, at least 1100%, at least 1150%, or at least 1200% greater than the AUC exhibited by the non-nanoparticulate formulation of metaxalone, administered at the same dosage.

29. (Original) The composition of claim 1 which does not produce significantly different absorption levels when administered under fed as compared to fasting conditions.

30. (Previously Presented) The composition of claim 29, wherein the difference in absorption of the metaxalone composition of the invention, when administered in the fed versus the fasted state, is selected from the group consisting of less than 100%, less than 90%, less than 80%, less than 70%, less than 60%, less than 50%, less than 40%, less than 30%, less than 25%, less than 20%, less than 15%, less than 10%, less than 5%, and less than 3%.

31. (Original) The composition of claim 1, wherein administration of the composition to a human in a fasted state is bioequivalent to administration of the composition to a subject in a fed state.

32. (Original) The composition of claim 31, wherein “bioequivalency” is established by:

- (a) a 90% Confidence Interval of between 0.80 and 1.25 for both C_{\max} and AUC; or
- (b) a 90% Confidence Interval of between 0.80 and 1.25 for AUC and a 90% Confidence Interval of between 0.70 to 1.43 for C_{\max} .

33. (Previously Presented) A method of making a metaxalone composition comprising contacting particles of metaxalone or a salt thereof with at least one surface stabilizer for a time and under conditions sufficient to provide a metaxalone composition having an effective average particle size of less than 2000 nm and having the surface stabilizer adsorbed on the surface of the metaxalone particles.

34. (Original) The method of claim 33, wherein said contacting comprises grinding, wet grinding, or homogenizing.

35. (Original) The method of claim 33, wherein said contacting comprises:
- (a) dissolving the particles of a metaxalone or a salt thereof in a solvent;
 - (b) adding the resulting metaxalone solution to a solution comprising at least one surface stabilizer; and
 - (c) precipitating the solubilized metaxalone having at least one surface stabilizer adsorbed on the surface thereof by the addition thereto of a non-solvent.

36. (Previously Presented) The method of claim 33, wherein the effective average particle size of the metaxalone particles is selected from the group consisting of less than 1900 nm, less than 1800 nm, less than 1700 nm, less than 1600 nm, less than 1500 nm, less than 1000 nm, less than 1400 nm, less than 1300 nm, less than 1200 nm, less than 1100 nm, less than 900

nm, less than 800 nm, less than 700 nm, less than 600 nm, less than 500 nm, less than 400 nm, less than 300 nm, less than 250 nm, less than 200 nm, less than 100 nm, less than 75 nm, and less than 50 nm.

37. (Previously Presented) A method of treating a subject in need comprising administering to the subject an effective amount of a composition comprising:

- (a) particles of a metaxalone or a salt thereof, wherein the metaxalone particles have an effective average particle size of less than 2000 nm; and
- (b) at least one surface stabilizer adsorbed to the surface of the metaxalone particles.

38. (Previously Presented) The method of claim 37, wherein the metaxalone or a salt thereof is selected from the group consisting of a crystalline phase, an amorphous phase, and a semi-crystalline phase.

39. (Previously Presented) The method of claim 37, wherein the effective average particle size of the metaxalone particles is selected from the group consisting of less than 1900 nm, less than 1800 nm, less than 1700 nm, less than 1600 nm, less than 1500 nm, less than 1400 nm, less than 1300 nm, less than 1200 nm, less than 1100 nm, less than 1000 nm, less than 900 nm, less than 800 nm, less than 700 nm, less than 600 nm, less than 500 nm, less than 400 nm, less than 300 nm, less than 250 nm, less than 200 nm, less than 100 nm, less than 75 nm, and less than 50 nm.

40. (Original) The method of claim 37, wherein the composition is formulated for administration selected from the group consisting of oral, pulmonary, rectal, ophthalmic, colonic, parenteral, intracisternal, intravaginal, intraperitoneal, local, buccal, nasal, and topical administration.

41. (Original) The method of claim 37, wherein the composition is a dosage form selected from the group consisting of liquid dispersions, oral suspensions, gels, aerosols, ointments, creams, controlled release formulations, fast melt formulations, lyophilized

formulations, tablets, capsules, delayed release formulations, extended release formulations, pulsatile release formulations, and mixed immediate release and controlled release formulations.

42. (Original) The method of claim 37, wherein the composition further comprises one or more pharmaceutically acceptable excipients, carriers, or a combination thereof.

43. (Original) The method of claim 37, wherein:

(a) the metaxalone or a salt thereof is present in an amount selected from the group consisting of from about 99.5% to about 0.001%, from about 95% to about 0.1%, and from about 90% to about 0.5%, by weight, based on the total combined weight of the metaxalone or a salt thereof and at least one surface stabilizer, not including other excipients; and

(b) the at least one surface stabilizer is present in an amount selected from the group consisting of from about 0.5% to about 99.999% by weight, from about 5.0% to about 99.9% by weight, and from about 10% to about 99.5% by weight, based on the total combined dry weight of the metaxalone or a salt thereof and at least one surface stabilizer, not including other excipients.

44. (Cancelled)

45. (Previously Presented) The method of claim 37, wherein the at least one surface stabilizer is selected from the group consisting of cetyl pyridinium chloride, gelatin, casein, phosphatides, dextran, glycerol, gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glycerol monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers, polyoxyethylene castor oils, polyoxyethylene sorbitan fatty acid esters, polyethylene glycols, dodecyl trimethyl ammonium bromide, polyoxyethylene stearates, colloidal silicon dioxide, phosphates, sodium dodecylsulfate, carboxymethylcellulose calcium, hydroxypropyl celluloses, hypromellose, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hypromellose phthalate, noncrystalline cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol,

polyvinylpyrrolidone, 4-(1,1,3,3-tetramethylbutyl)-phenol polymer with ethylene oxide and formaldehyde, poloxamers; poloxamines, a charged phospholipid, dioctylsulfosuccinate, dialkylesters of sodium sulfosuccinic acid, sodium lauryl sulfate, alkyl aryl polyether sulfonates, mixtures of sucrose stearate and sucrose distearate, p-isononylphenoxypoly-(glycidol), decanoyl-N-methylglucamide; n-decyl β -D-glucopyranoside; n-decyl β -D-maltopyranoside; n-dodecyl β -D-glucopyranoside; n-dodecyl β -D-maltoside; heptanoyl-N-methylglucamide; n-heptyl- β -D-glucopyranoside; n-heptyl β -D-thioglucoside; n-hexyl β -D-glucopyranoside; nonanoyl-N-methylglucamide; n-noyl β -D-glucopyranoside; octanoyl-N-methylglucamide; n-octyl- β -D-glucopyranoside; octyl β -D-thioglucopyranoside; lysozyme, PEG-phospholipid, PEG-cholesterols, PEG-vitamin A, PEG-vitamin E, random copolymers of vinyl acetate and vinyl pyrrolidone, cationic polymers, cationic biopolymers, cationic polysaccharides, cationic cellulosics, cationic alginates, cationic nonpolymeric compounds, cationic phospholipids, benzalkonium chloride, polymethylmethacrylate trimethylammonium bromide, polyvinylpyrrolidone-2-dimethylaminoethyl methacrylate dimethyl sulfate, hexadecyltrimethyl ammonium bromide, cationic lipids, sulfonium compounds, phosphonium compounds, quaternary ammonium compounds, benzyl-di(2-chloroethyl)ethylammonium bromide, coconut trimethyl ammonium chloride, coconut trimethyl ammonium bromide, coconut methyl dihydroxyethyl ammonium chloride, coconut methyl dihydroxyethyl ammonium bromide, decyl triethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride bromide, C₁₂₋₁₅dimethyl hydroxyethyl ammonium chloride, C₁₂₋₁₅dimethyl hydroxyethyl ammonium chloride bromide, coconut dimethyl hydroxyethyl ammonium chloride, coconut dimethyl hydroxyethyl ammonium bromide, myristyl trimethyl ammonium methyl sulphate, lauryl dimethyl benzyl ammonium chloride, lauryl dimethyl benzyl ammonium bromide, lauryl dimethyl (ethenoxy)₄ ammonium chloride, lauryl dimethyl (ethenoxy)₄ ammonium bromide, N-alkyl (C₁₂₋₁₈)dimethylbenzyl ammonium chloride, N-alkyl (C₁₄₋₁₈)dimethyl-benzyl ammonium chloride, N-tetradecylidmethylbenzyl ammonium chloride monohydrate, dimethyl didecyl ammonium chloride, N-alkyl and (C₁₂₋₁₄) dimethyl 1-

naphthylmethyl ammonium chloride, trimethylammonium halide, alkyl-trimethylammonium salts, dialkyl-dimethylammonium salts, lauryl trimethyl ammonium chloride, ethoxylated alkyamidoalkyldialkylammonium salt, an ethoxylated trialkyl ammonium salt, dialkylbenzene dialkylammonium chloride, N-didecyldimethyl ammonium chloride, N-tetradecyldimethylbenzyl ammonium, chloride monohydrate, N-alkyl(C₁₂₋₁₄) dimethyl 1-naphthylmethyl ammonium chloride, dodecyldimethylbenzyl ammonium chloride, dialkyl benzenealkyl ammonium chloride, lauryl trimethyl ammonium chloride, alkylbenzyl methyl ammonium chloride, alkyl benzyl dimethyl ammonium bromide, C₁₂ trimethyl ammonium bromides, C₁₅ trimethyl ammonium bromides, C₁₇ trimethyl ammonium bromides, dodecylbenzyl triethyl ammonium chloride, polydiallyldimethylammonium chloride (DADMAC), dimethyl ammonium chlorides, alkyldimethylammonium halogenides, tricetyl methyl ammonium chloride, decyltrimethylammonium bromide, dodecyltriethylammonium bromide, tetradecyltrimethylammonium bromide, methyl trioctylammonium chloride, polyquaternium 10, tetrabutylammonium bromide, benzyl trimethylammonium bromide, choline esters, benzalkonium chloride, stearalkonium chloride compounds, cetyl pyridinium bromide, cetyl pyridinium chloride, halide salts of quaternized polyoxyethylalkylamines, quaternized ammonium salt polymers, alkyl pyridinium salts; amines, amine salts, amine oxides, imide azolinium salts, protonated quaternary acrylamides, methylated quaternary polymers, and cationic guar.

46. (Previously Presented) The method of claim 37, wherein the composition is bioadhesive.

47. (Original) The method of claim 45, wherein the composition is bioadhesive.

48. (Original) The method of claim 37, comprising at least one primary surface stabilizer and at least one secondary surface stabilizer.

49. (Original) The method of claim 37, comprising as surface stabilizers polyvinylpyrrolidone, docusate sodium, lysozyme, or a combination thereof.

50. (Original) The method of claim 49, comprising as surface stabilizers polyvinylpyrrolidone and docusate sodium.

51. (Original) The method of claim 37, additionally comprising administering one or more non-metaxalone active agents.

52. (Original) The method of claim 51, wherein said additionally one or more non-metaxalone active agents are selected from the group consisting of amino acids, proteins, peptides, nucleotides, anti-obesity drugs, central nervous system stimulants, carotenoids, corticosteroids, elastase inhibitors, anti-fungals, oncology therapies, anti-emetics, analgesics, cardiovascular agents, anti-inflammatory agents, anthelmintics, anti-arrhythmic agents, antibiotics, anticoagulants, antidepressants, antidiabetic agents, antiepileptics, antihistamines, antihypertensive agents, antimuscarinic agents, antimycobacterial agents, antineoplastic agents, immunosuppressants, antithyroid agents, antiviral agents, anxiolytics, sedatives, astringents, alpha-adrenergic receptor blocking agents, beta-adrenoceptor blocking agents, blood products, blood substitutes, cardiac inotropic agents, contrast media, corticosteroids, cough suppressants, diagnostic agents, diagnostic imaging agents, diuretics, dopaminergics, haemostatics, immunological agents, lipid regulating agents, muscle relaxants, parasympathomimetics, parathyroid calcitonin, parathyroid biphosphonates, prostaglandins, radio-pharmaceuticals, sex hormones, anti-allergic agents, stimulants, anoretics, sympathomimetics, thyroid agents, vasodilators, xanthines, acyclovir, alprazolam, altretamine, amiloride, amiodarone, benztropine mesylate, bupropion, cabergoline, candesartan, cerivastatin, chlorpromazine, ciprofloxacin, cisapride, clarithromycin, clonidine, clopidogrel, cyclobenzaprine, cyproheptadine, delavirdine, desmopressin, diltiazem, dipyridamole, dolasetron, enalapril maleate, enalaprilat, famotidine, felodipine, furazolidone, glipizide, irbesartan, ketoconazole, lansoprazole, loratadine, loxapine, mebendazole, mercaptopurine, milrinone lactate, minocycline, mitoxantrone, nelfinavir mesylate,

nimodipine, norfloxacin, olanzapine, omeprazole, penciclovir, pimozide, tacolimus, quazepam, raloxifene, rifabutin, rifampin, risperidone, rizatriptan, saquinavir, sertraline, sildenafil, acetyl-sulfisoxazole, temazepam, thiabendazole, thioguanine, trandolapril, triamterene, trimetrexate, troglitazone, trovafloxacin, verapamil, vinblastine sulfate, mycophenolate, atovaquone, atovaquone, proguanil, ceftazidime, cefuroxime, etoposide, terbinafine, thalidomide, fluconazole, amsacrine, dacarbazine, teniposide, acetylsalicylate, an NSAID, and a COX-2 inhibitor.

53. (Original) The method of claim 52, wherein the NSAID is selected from the group consisting of nabumetone, tiaramide, proquazone, bufexamac, flumizole, epirazole, tinoridine, timegadine, dapsone, aspirin, diflunisal, benorylate, fosfosal, diclofenac, alclofenac, fenclofenac, etodolac, indomethacin, sulindac, tolmetin, fentiazac, tilomisole, carprofen, fenbufen, flurbiprofen, ketoprofen, oxaprozin, suprofen, tiaprofenic acid, ibuprofen, naproxen, fenoprofen, indoprofen, piroprofen, flufenamic, mefenamic, meclofenamic, niflumic, oxyphenbutazone, phenylbutazone, apazone, feprazone, piroxicam, sudoxicam, isoxicam, and tenoxicam.

54. (Previously Presented) The method of claim 52, wherein the COX-2 inhibitor is selected from the group consisting of celecoxib, rofecoxib, meloxicam, valdecoxib, parecoxib, etoricoxib, 4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]benzene-sulfonamide, N-(2-cyclohexyloxy-4-nitrophenyl)methanesulfonamide, 5-(4-fluorophenyl)-1-[4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)-1*H*-pyrazole, 1-fluoro-4-(2-(4-(methylsulfonyl)phenyl)-3-(trifluoromethyl)-1*H*-pyrazole)cyclopent-1-enyl)benzene, 4-[5-(4-bromophenyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]-benzenesulfonamide, 5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-trifluoromethylpyrazole, etodolac, (5,5-dimethyl-3-(3-fluorophenyl)-4-(4-methylsulfonyl)phenyl 2(5*H*)-furanone), monteleukast, 5-methanesulfonamido-6-(2,4-difluorothiophenyl)-1-indanone, (R)-1-[(4-bromophenyl)methyl]-5-methoxy- β ,2-dimethyl-1*H*-indole-3-butanoic acid, 1-[(4-bromophenyl)methyl]-5-methoxy- β ,2-dimethyl-1*H*-indole-3-butanoic acid, 5-methoxy-2-methyl-1-(2,4,6-trichlorobenzoyl)-1*H*-indole-3-acetic acid, 5-bromo-2-(4-fluorophenyl)-3-(4-

(methylsulfonyl)phenyl)thiophene, 1-(7-tert-butyl-2,3-dihydro-3,3-dimethylbenzo(b)furan-5-yl)-4-cyclopropylbutan-1-one, iguratimod, 4-[[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]methylene]dihydro-2-methyl-2H-1,2-oxazin-3(4H)-one, acetyldiphenylalanyl-leucyl-aspartyl-isoleucyl-isoleucyl-tryptophan, acetyl-(5H-dibenzyl(a,d)cycloheptene-10,11-dihydroglycine-leucyl-aspartyl-isoleucyl-isoleucyl-tryptophan), 5-(3,5-di-tert-butyl-4-hydroxybenzylidene)-2-(methoxyamino)thiazol-4-one, flurbiprofen, nimesulide, nabumetone, flosulide, piroxicam, diclofenac, lumiracoxib, diflumidone, 4-(4-cyclohexyl-2-methyl-5-oxazolyl)-2-fluoro-benzenesulfonamide, 4'-acetyl-2'-(2,4-difluorophenoxy)methanesulfonanilide, N-[5-(4-fluorophenoxy)-2-thienyl]-methanesulfonamide, 5-(4-chlorophenyl)-N-hydroxy-1-(4-methoxyphenyl)-N-methyl-1H-pyrazole-3-propanamide, N-[6-(2,4-difluorophenoxy)-2,3-dihydro-1-oxo-1H-inden-5-yl]-methanesulfonamide, a mixture of 2,6-bis(1,1-dimethylethyl)-4-[(E)-(2-ethyl-1,1-dioxido-5-isothiazolidinylidene)methyl]-phenol and 9,13b-dihydro-1H-dibenz[c,f]imidazo[1,5-a]azepin-3-amine hydrochloride, 6-[[5-(4-chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-yl]methyl]-3(2H)-pyridazinone, 5-(4-chlorobenzoyl)-N-[(4-iodophenyl)sulfonyl]-1,4-dimethyl-1H-pyrrole-2-carboxamide 7-(3-(4-acetyl-3-methoxy-2-propylphenoxy)propoxy)-3,4-dihydro-8-propyl-2H-1-benzopyran-2-carboxylic acid, pranlukast, and 3-(2-(carboxymethoxy)-4-methoxyphenyl)-1-(3,4-(methylenedioxy)phenyl)-5-(prop-1-yloxy)indan-2-carboxylic acid, heptynylsulfide, and 3-(difluoromethyl)-1-(4-methoxyphenyl)-5-[4-(methylsulfinyl)phenyl]-1H-pyrazole.

55. (Original) The method of claim 37, wherein the T_{\max} of the metaxalone, when assayed in the plasma of a mammalian subject following administration, is less than the T_{\max} for a non-nanoparticulate metaxalone formulation, administered at the same dosage.

56. (Previously Presented) The method of claim 55, wherein the T_{\max} is selected from the group consisting of not greater than 90%, not greater than 80%, not greater than 70%, not greater than 60%, not greater than 50%, not greater than 30%, not greater than 25%, not greater

than 20%, not greater than 15%, not greater than 10%, and not greater than 5% of the T_{\max} exhibited by a non-nanoparticulate metaxalone formulation, administered at the same dosage.

57. (Original) The method of claim 37, wherein the C_{\max} of the metaxalone, when assayed in the plasma of a mammalian subject following administration, is greater than the C_{\max} for a non-nanoparticulate metaxalone formulation, administered at the same dosage.

58. (Previously Presented) The method of claim 57, wherein the C_{\max} is selected from the group consisting of at least 50%, at least 100%, at least 200%, at least 300%, at least 400%, at least 500%, at least 600%, at least 700%, at least 800%, at least 900%, at least 1000%, at least 1100%, at least 1200%, at least 1300%, at least 1400%, at least 1500%, at least 1600%, at least 1700%, at least 1800%, or at least 1900% greater than the C_{\max} exhibited by a non-nanoparticulate formulation of metaxalone, administered at the same dosage.

59. (Original) The method of claim 37, wherein the AUC of the metaxalone, when assayed in the plasma of a mammalian subject following administration, is greater than the AUC for a non-nanoparticulate metaxalone formulation, administered at the same dosage.

60. (Previously Presented) The method of claim 59, wherein the AUC is selected from the group consisting of at least 25%, at least 50%, at least 75%, at least 100%, at least 125%, at least 150%, at least 175%, at least 200%, at least 225%, at least 250%, at least 275%, at least 300%, at least 350%, at least 400%, at least 450%, at least 500%, at least 550%, at least 600%, at least 750%, at least 700%, at least 750%, at least 800%, at least 850%, at least 900%, at least 950%, at least 1000%, at least 1050%, at least 1100%, at least 1150%, or at least 1200% greater than the AUC exhibited by the non-nanoparticulate formulation of metaxalone, administered at the same dosage.

61. (Original) The method of claim 37, wherein the metaxalone composition does not produce significantly different absorption levels when administered under fed as compared to fasting conditions.

62. (Previously Presented) The method of claim 61, wherein the difference in absorption of the metaxalone composition of the invention, when administered in the fed versus the fasted state, is selected from the group consisting of less than 100%, less than 90%, less than 80%, less than 70%, less than 60%, less than 50%, less than 40%, less than 30%, less than a25%, less than 20%, less than 15%, less than 10%, less than 5%, and less than 3%.

63. (Original) The method of claim 37, wherein administration of the composition to a human in a fasted state is bioequivalent to administration of the composition to a human in a fed state.

64. (Original) The method of claim 63, wherein “bioequivalency” is established by:
(a) a 90% Confidence Interval of between 0.80 and 1.25 for both C_{max} and AUC; or
(b) a 90% Confidence Interval of between 0.80 and 1.25 for AUC and a 90% Confidence Interval of between 0.70 to 1.43 for C_{max} .

65. (Original) The method of claim 37, wherein the subject is a human.

66. (Original) The method of claim 37, wherein the method is used to treat an indication selected from the group consisting of indications where musculoskeletal relaxants are typically used, severe musculoskeletal strains, severe musculoskeletal sprains, musculoskeletal trauma, cervical radiculopathy, lumbar radiculopathy, degenerative osteoarthritis, herniated disk, spondylitis, laminectomy, and a combination thereof.

67. (Previously Presented) The composition of claim 1, wherein the surface stabilizer is selected from the group consisting of an anionic surface stabilizer, a cationic surface stabilizer, a zwitterionic surface stabilizer, and a nonionic surface stabilizer.

68. (Previously Presented) The method of claim 37, wherein the surface stabilizer is selected from the group consisting of an anionic surface stabilizer, a cationic surface stabilizer, a zwitterionic surface stabilizer, and a nonionic surface stabilizer.

AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions, and listings, of claims in the application.

Listing of Claims

1. (Previously Presented) A nanoparticulate sildenafil free base composition comprising:
 - (a) particles of sildenafil free base having an effective average particle size of less than 2000 nm; and
 - (b) at least one surface stabilizer,wherein the composition is bioequivalent when administered under fed and fasted conditions.
2. (Previously Presented) The composition of claim 1, wherein upon administration the composition has an AUC that differs between the fed and fasted states by an amount selected from the group consisting of less than 25%, less than 20%, less than 15%, less than 10%, less than 5%, less than 3%, and less than 1%.
3. (Cancelled)
4. (Previously Presented) The composition of claim 1, wherein upon administration the composition has a T_{max} that differs between the fed and fasted states by an amount selected from the group consisting of less than 60%, less than 50%, less than 40%, less than 30%, less than 20%, less than 15%, less than 10%, less than 5%, and less than 3%.
5. (Cancelled)
6. (Previously Presented) The composition of claim 1, wherein upon administration the composition has a C_{max} that differs between the fed and fasted states by an amount selected from the group consisting of less than 40%, less than 30%, less than 20%, less than 15%, less than 10%, less than 5%, and less than 3%.

7. (Previously Presented) The composition of claim 1, wherein sildenafil free base is selected from the group consisting of a crystalline phase, an amorphous phase, a semi-crystalline phase, and mixtures thereof.
8. (Previously Presented) The composition of claim 1, wherein the effective average particle size of sildenafil free base is selected from the group consisting of less than 1900 nm, less than 1800 nm, less than 1700 nm, less than 1600 nm, less than 1500 nm, less than 1400 nm, less than 1300 nm, less than 1200 nm, less than 1100 nm, less than 1000 nm, less than 900 nm, less than 800 nm, less than 700 nm, less than 600 nm, less than 500 nm, less than 400 nm, less than 300 nm, less than 250 nm, less than 200 nm, less than 100 nm, less than 75 nm, and less than 50 nm.
9. (Previously Presented) The composition of claim 1, wherein the composition is formulated for administration selected from the group consisting of oral, pulmonary, rectal, ophthalmic, colonic, parenteral, intracisternal, intravaginal, intraperitoneal, local, buccal, nasal, and topical administration.
10. (Original) The composition of claim 1, wherein the composition is formulated into a dosage form selected from the group consisting of liquid dispersions, gels, aerosols, ointments, creams, controlled release formulations, fast melt formulations, lyophilized formulations, tablets, capsules, delayed release formulations, extended release formulations, pulsatile release formulations, and mixed immediate release and controlled release formulations.
11. (Original) The composition of claim 1, formulated into an aerosol or nasal spray and having a T_{\max} which is less than that observed with a composition of non-nanoparticulate sildenafil.
12. (Original) The composition of claim 1, wherein the composition further comprises one or more pharmaceutically acceptable excipients, carriers, or a combination thereof.

13. (Previously Presented) The composition of claim 1, wherein sildenafil free base is present in an amount selected from the group consisting of from 99.5% to 0.001%, from 95% to 0.1%, and from 90% to 0.5%, by weight, based on the total combined dry weight of sildenafil free base and at least one surface stabilizer, not including other excipients.

14. (Original) The composition of claim 1, wherein the at least one surface stabilizer is present in an amount selected from the group consisting of from about 0.5% to about 99.999%, from about 5.0% to about 99.9%, or from about 10% to about 99.5%, by weight, based on the total combined dry weight of the sildenafil free base and at least one surface stabilizer, not including other excipients.

15. (Original) The composition of claim 1, comprising at least two surface stabilizers.

16. (Original) The composition of claim 1, wherein the surface stabilizer is selected from the group consisting of an anionic surface stabilizer, a cationic surface stabilizer, an ionic surface stabilizer, and a zwitterionic surface stabilizer.

17. (Previously Presented) The composition of claim 16, wherein at least one surface stabilizer is selected from the group consisting of cetyl pyridinium chloride, gelatin, casein, phosphatides, dextran, glycerol, gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glycerol monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers, polyoxyethylene castor oil, polyoxyethylene sorbitan fatty acid esters, polyethylene glycols, dodecyl trimethyl ammonium bromide, polyoxyethylene stearates, colloidal silicon dioxide, phosphates, sodium dodecylsulfate, carboxymethylcellulose calcium, hydroxypropyl celluloses, hydroxypropyl methylcellulose, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hydroxypropylmethylcellulose phthalate, noncrystalline cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol, polyvinylpyrrolidone, 4-(1,1,3,3-tetramethylbutyl)-phenol polymer with ethylene oxide and formaldehyde, poloxamers, poloxamines, a charged phospholipid, dioctylsulfosuccinate, dialkylesters of sodium sulfosuccinic acid, sodium lauryl sulfate, alkyl aryl polyether sulfonates, mixtures of sucrose

stearate and sucrose distearate, $C_{18}H_{37}CH_2C(O)N(CH_3)-CH_2(CHOH)_4(CH_2OH)_2$, p-isononylphenoxypoly(glycidol), decanoyl-N-methylglucamide, n-decyl β -D-glucopyranoside, n-decyl β -D-maltopyranoside, n-dodecyl β -D-glucopyranoside, n-dodecyl β -D-maltoside, heptanoyl-N-methylglucamide, n-heptyl- β -D-glucopyranoside, n-heptyl β -D-thioglucoside, n-hexyl β -D-glucopyranoside, nonanoyl-N-methylglucamide, n-nonyl β -D-glucopyranoside, octanoyl-N-methylglucamide, n-octyl- β -D-glucopyranoside, octyl β -D-thioglucopyranoside, lysozyme, PEG-phospholipid, PEG-cholesterol, PEG-vitamin A, PEG-vitamin E, and random copolymers of vinyl acetate and vinyl pyrrolidone.

18. (Previously Presented) The composition of claim 16, wherein the surface stabilizer is selected from the group consisting of cationic lipids, polymethylmethacrylate trimethylammonium bromide, sulfonium compounds, polyvinylpyrrolidone-2-dimethylaminoethyl methacrylate dimethyl sulfate, hexadecyltrimethyl ammonium bromide, phosphonium compounds, quarternary ammonium compounds, benzyl-di(2-chloroethyl)ethylammonium bromide, coconut trimethyl ammonium chloride, coconut trimethyl ammonium bromide, coconut methyl dihydroxyethyl ammonium chloride, coconut methyl dihydroxyethyl ammonium bromide, decyl triethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride bromide, C_{12-15} dimethyl hydroxyethyl ammonium chloride, C_{12-15} dimethyl hydroxyethyl ammonium chloride bromide, coconut dimethyl hydroxyethyl ammonium chloride, coconut dimethyl hydroxyethyl ammonium bromide, myristyl trimethyl ammonium methyl sulphate, lauryl dimethyl benzyl ammonium chloride, lauryl dimethyl benzyl ammonium bromide, lauryl dimethyl (ethenoxy)₄ ammonium chloride, lauryl dimethyl (ethenoxy)₄ ammonium bromide, N-alkyl (C_{12-18})dimethylbenzyl ammonium chloride, N-alkyl (C_{14-18})dimethylbenzyl ammonium chloride, N-tetradecyldimethylbenzyl ammonium chloride monohydrate, dimethyl dodecylammonium chloride, N-alkyl and (C_{12-14}) dimethyl 1-naphthylmethyl ammonium chloride, trimethylammonium halide, alkyl-trimethylammonium salts, dialkyl-dimethylammonium salts, lauryl trimethyl ammonium chloride, ethoxylated alkyamidoalkyldialkylammonium salt, an ethoxylated trialkyl ammonium salt, dialkylbenzene dialkylammonium chloride, N-dodecyldimethyl ammonium chloride, N-

tetradecyldimethylbenzyl ammonium, chloride monohydrate, N-alkyl(C₁₂₋₁₄) dimethyl 1-naphthylmethyl ammonium chloride, dodecyldimethylbenzyl ammonium chloride, dialkyl benzenealkyl ammonium chloride, lauryl trimethyl ammonium chloride, alkylbenzyl methyl ammonium chloride, alkyl benzyl dimethyl ammonium bromide, C₁₂ trimethyl ammonium bromides, C₁₅ trimethyl ammonium bromides, C₁₇ trimethyl ammonium bromides, dodecylbenzyl triethyl ammonium chloride, poly-diallyldimethylammonium chloride dimethyl ammonium chlorides, alkyldimethylammonium halogenides, tricetyl methyl ammonium chloride, decyltrimethylammonium bromide, dodecyltriethylammonium bromide, tetradecyltrimethylammonium bromide, methyl trioctylammonium chloride, polyquaternium 10, tetrabutylammonium bromide, benzyl trimethylammonium bromide, choline esters, benzalkonium chloride, stearalkonium chloride compounds, cetyl pyridinium bromide, cetyl pyridinium chloride, halide salts of quaternized polyoxyethylalkylamines, quaternized ammonium salt polymers, alkyl pyridinium salts, amines, amine salts, amine oxides, imide azolinium salts, protonated quaternary acrylamides, methylated quaternary polymers, and cationic guar.

19. (Original) The composition of claim 18, wherein the composition is bioadhesive.

20. (Original) The composition of claim 1, wherein the surface stabilizer is selected from the group consisting of hydroxypropylmethylcellulose (HPMC), docusate sodium, and a combination thereof.

21. (Previously Presented) The composition of claim 1, additionally comprising at least one nanoparticulate sildenafil free base composition having an effective average particle size of less than 2 microns, wherein said additional nanoparticulate sildenafil free base composition has an effective average particle size which is different than the particle size of the nanoparticulate sildenafil free base composition of claim 1.

22. (Original) The composition of claim 1, additionally comprising at least one non-sildenafil free base active agent.

23. (Previously Presented) The composition of claim 22, wherein the non-sildenafil free base active agent is selected from the group consisting of alpha adrenergic receptor blocking agents, delaquamine, phenotolamine, doxazosin, prostaglandins, alprostadil, misoprostol, testosterone, antidepressants, trazodone, apomorphine, NO donors, and central nervous system stimulants.

24. (Previously Presented) The composition of claim 22, wherein said active agent is selected from the group consisting of PDE5 inhibitors, amino acids, proteins, peptides, nucleotides, anti-obesity drugs, nutraceuticals, dietary supplements, central nervous system stimulants, carotenoids, corticosteroids, elastase inhibitors, anti-fungals, alkylxanthine, oncology therapies, anti-emetics, analgesics, opioids, antipyretics, cardiovascular agents, anti-inflammatory agents, anthelmintics, anti-arrhythmic agents, antibiotics, anticoagulants, antidepressants, antidiabetic agents, antiepileptics, antihistamines, antihypertensive agents, antimuscarinic agents, antimycobacterial agents, antineoplastic agents, immunosuppressants, antithyroid agents, antiviral agents, anxiolytics, sedatives, astringents, alpha-adrenergic receptor blocking agents, beta-adrenoceptor blocking agents, blood products, blood substitutes, cardiac inotropic agents, contrast media, corticosteroids, cough suppressants, diagnostic agents, diagnostic imaging agents, diuretics, dopaminergics, haemostatics, immunological agents, lipid regulating agents, muscle relaxants, parasympathomimetics, parathyroid hormones, calcitonin, biphosphonates, prostaglandins, radio-pharmaceuticals, sex hormones, anti-allergic agents, stimulants, anoretics, sympathomimetics, thyroid agents, vasodilators, vasomodulator, xanthines, mu receptor antagonists, kappa receptor antagonists, non-narcotic analgesics, monoamine uptake inhibitors, adenosine regulating agents, cannabinoid, Substance P antagonists, neurokinin-1 receptor antagonists, and sodium channel blockers.

25. (Original) The composition of claim 24, wherein the nutraceutical is selected from the group consisting of yohimbine, *Cornus officinalis*, *Cinnamomum aromaticum*, *Panax ginseng* and *Pulsatilla pratensis*.

26. (Original) The composition of claim 24, wherein the amino acid is L-arginine.

27. (Original) The composition of claim 24, wherein the non-sildenafil free base PDE5 inhibitor is selected from the group consisting of vardenafil, tadalafil, TA-1790, UK-114542, Compound 14, EMD221829, EMR 62 203, T-1032, M-54033, M-54018, and E-4010.

28. (Previously Presented) The composition of any one of claims 22-27, wherein at least one non-sildenafil free base active agent has an effective average particle size of less than 2 microns.

29. (Previously Presented) The composition of any one of claims 22-27, wherein at least one non-sildenafil free base active agent has an effective average particle size of greater than 2 microns.

30. (Previously Presented) The composition of claim 1, wherein upon administration the composition redisperses such that the sildenafil free base particles have a particle size selected from the group consisting of less than 2 microns, less than 1900 nm, less than 1800 nm, less than 1700 nm, less than 1600 nm, less than 1500 nm, less than 1400 nm, less than 1300 nm, less than 1200 nm, less than 1100 nm, less than 1000 nm, less than 900 nm, less than 800 nm, less than 700 nm, less than 600 nm, less than 500 nm, less than 400 nm, less than 300 nm, less than 250 nm, less than 200 nm, less than 150 nm, less than 100 nm, less than 75 nm, and less than 50 nm.

31. (Previously Presented) The composition of claim 1, wherein upon administration the composition has a T_{max} less than that of a composition of non-nanoparticulate sildenafil or a composition of nanoparticulate sildenafil citrate, administered at the same dosage.

32. (Previously Presented) The composition of claim 31, wherein in comparative pharmacokinetic testing with a composition of non-nanoparticulate sildenafil or a composition of nanoparticulate sildenafil citrate, the nanoparticulate sildenafil free base composition, administered at the same dosage, exhibits a T_{max} which is selected from the group consisting of less than 200%, less than 175%, less than 150%, less than 125%, less than 100%, less than 90%, less than 80%, less than 70%, less than 60%, less than 50%, less than

40%, less than 30%, less than 25%, less than 20%, less than 15%, and less than 10% of the T_{\max} exhibited by the composition of non-nanoparticulate sildenafil or the composition of nanoparticulate sildenafil citrate.

33. (Previously Presented) The composition of claim 1, wherein upon administration to a human the composition has a T_{\max} selected from the group consisting of less than 1.5 hours, less than 1.25 hours, less than 1.0 hours, less than 50 minutes, less than 40 minutes, less than 45 minutes, less than 35 minutes, less than 30 minutes, less than 25 minutes, less than 20 minutes, less than 15 minutes, and less than 10 minutes.

34. (Previously Presented) The composition of claim 1, wherein upon administration the composition has a C_{\max} greater than the C_{\max} of a composition of non-nanoparticulate sildenafil or a composition of nanoparticulate sildenafil citrate, administered at the same dosage.

35. (Previously Presented) The composition of claim 34, wherein in comparative pharmacokinetic testing with a composition of non-nanoparticulate sildenafil or a composition of nanoparticulate sildenafil citrate, the nanoparticulate sildenafil free base composition, administered at the same dosage, exhibits a C_{\max} which is selected from the group consisting of greater than 5%, greater than 10%, greater than 15%, greater than 20%, greater than 30%, greater than 40%, greater than 50%, greater than 60%, greater than 70%, greater than 80%, greater than 90%, greater than 100%, greater than 110%, greater than 120%, greater than 130%, greater than 140%, and greater than 150% of the C_{\max} exhibited by the composition of non-nanoparticulate sildenafil or the composition of nanoparticulate sildenafil citrate.

36. (Previously Presented) The composition of claim 1, wherein administration of a 100 mg oral dose of the nanoparticulate sildenafil free base composition, in a healthy adult male, results in a mean C_{\max} of greater than 440 ng/mL, a T_{\max} of less than 60 minutes, or a combination thereof.

37. (Previously Presented) The composition of claim 1, wherein administration of a 100 mg oral dose of the nanoparticulate sildenafil free base composition produces a C_{\max}

which is selected from the group consisting of greater than 440 ng/mL, greater than 450 ng/mL, greater than 500 ng/mL, greater than 550 ng/mL, greater than 600 ng/mL, greater than 650 ng/mL, greater than 700 ng/mL, greater than 750 ng/mL, greater than 800 ng/mL, greater than 850 ng/mL, greater than 900 ng/mL, greater than 950 ng/mL, greater than 1000 ng/mL, greater than 1050 ng/mL, greater than 1100 ng/mL, greater than 1150 ng/mL, greater than 1200 ng/mL, greater than 1250 ng/mL, greater than 1300 ng/mL, greater than 1350 ng/mL, and greater than 1400 ng/mL.

38. (Previously Presented) The composition of claim 1, wherein upon administration the composition has an AUC greater than the AUC of a composition of non-nanoparticulate sildenafil or a composition of nanoparticulate sildenafil citrate, administered at the same dosage.

39. (Previously Presented) The composition of claim 1, wherein in comparative pharmacokinetic testing with a composition of non-nanoparticulate sildenafil or a composition of nanoparticulate sildenafil citrate, the nanoparticulate sildenafil free base composition, administered at the same dosage, exhibits an AUC which is selected from the group consisting of greater than 5%, greater than 10%, greater than 15%, greater than 20%, greater than 30%, greater than 40%, greater than 50%, greater than 60%, greater than 70%, greater than 80%, greater than 90%, greater than 100%, greater than 110%, greater than 120%, greater than 130%, greater than 140%, and greater than 150% of the AUC exhibited by the composition of non-nanoparticulate sildenafil or the composition of nanoparticulate sildenafil citrate.

40. (Previously Presented) A method of making a nanoparticulate sildenafil free base composition comprising contacting particles of sildenafil free base with at least one surface stabilizer for a time and under conditions sufficient to provide a composition comprising sildenafil free base particles having an effective average particle size of less than 2 microns, wherein the resultant nanoparticulate sildenafil free base composition is bioequivalent when administered under fed and fasted conditions.

41. (Original) The method of claim 40, wherein said contacting comprises grinding.
42. (Original) The method of claim 41, wherein said grinding comprises wet grinding.
43. (Original) The method of claim 40, wherein said contacting comprises homogenizing.
44. (Original) The method of claim 40, wherein said contacting comprises:
- (a) dissolving the sildenafil free base particles in a solvent;
 - (b) adding the resulting sildenafil free base solution to a solution comprising at least one surface stabilizer; and
 - (c) precipitating the solubilized sildenafil free base having at least one surface stabilizer associated with the surface thereof by the addition thereto of a non-solvent.
45. (Previously Presented) The method of claim 40, wherein the nanoparticulate sildenafil free base composition upon administration has an AUC that differs between the fed and fasted state by an amount selected from the group consisting of less than 25%, less than 20%, less than 15%, less than 10%, less than 5%, less than 3%, and less than 1%.
46. (Cancelled)
47. (Previously Presented) The method of claim 40, wherein upon administration the composition has a T_{max} that differs between the fed and fasted state by an amount selected from the group consisting of less than 60%, less than 50%, less than 40%, less than 30%, less than 20%, less than 15%, less than 10%, less than 5%, and less than 3%.
48. (Cancelled)
49. (Previously Presented) The method of claim 40, wherein upon administration the composition has a C_{max} that differs between the fed and fasted state by an amount selected from the group consisting of less than 40%, less than 30%, less than 20%, less than 15%, less than 10%, less than 5%, and less than 3%.

50. (Previously Presented) The method of claim 40, wherein sildenafil free base is selected from the group consisting of a crystalline phase, an amorphous phase, a semi-crystalline phase, and mixtures thereof.

51. (Previously Presented) The method of claim 40, wherein the effective average particle size of the sildenafil free base particles is selected from the group consisting of less than 1900 nm, less than 1800 nm, less than 1700 nm, less than 1600 nm, less than 1500 nm, less than 1400 nm, less than 1300 nm, less than 1200 nm, less than 1100 nm, less than 1000 nm, less than 900 nm, less than 800 nm, less than 700 nm, less than 600 nm, less than 500 nm, less than 400 nm, less than 300 nm, less than 250 nm, less than 200 nm, less than 100 nm, less than 75 nm, and less than 50 nm.

52. (Original) The method of claim 40, wherein sildenafil free base is present in an amount selected from the group consisting of from about 99% to about 0.001%, from about 95% to about 0.5%, and from about 90% to about 0.5%, by weight, based on the total combined dry weight of sildenafil free base and at least one surface stabilizer, not including other excipients.

53. (Original) The method of claim 40, wherein at least one surface stabilizer is present in an amount selected from the group consisting of from about 0.5% to about 99.999%, from about 5.0% to about 99.9%, or from about 10% to about 99.5%, by weight, based on the total combined dry weight of the sildenafil free base and at least one surface stabilizer, not including other excipients.

54. (Original) The method of claim 40, wherein the sildenafil free base particles are contacted with at least two surface stabilizers.

55. (Original) The method of claim 40, wherein the surface stabilizer is selected from the group consisting of an anionic surface stabilizer, a cationic surface stabilizer, an ionic surface stabilizer, and a zwitterionic surface stabilizer.

56. (Previously Presented) The method of claim 55, wherein at least one surface stabilizer is selected from the group consisting of cetyl pyridinium chloride, gelatin, casein,

phosphatides, dextran, glycerol, gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glycerol monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers, polyoxyethylene castor oil, polyoxyethylene sorbitan fatty acid esters, polyethylen glycols, dodecyl trimethyl ammonium bromide, polyoxyethylene stearates, colloidal silicon dioxide, phosphates, sodium dodecylsulfate, carboxymethylcellulose calcium, hydroxypropyl celluloses, hydroxypropyl methylcellulose, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hydroxypropylmethyl-cellulose phthalate, noncrystalline cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol, polyvinylpyrrolidone, 4-(1,1,3,3-tetramethylbutyl)-phenol polymer with ethylene oxide and formaldehyde, poloxamers, poloxamines, a charged phospholipid, dioctylsulfosuccinate, dialkylesters of sodium sulfosuccinic acid, sodium lauryl sulfate, alkyl aryl polyether sulfonates, mixtures of sucrose stearate and sucrose distearate, $C_{18}H_{37}CH_2C(O)N(CH_3)-CH_2(CHOH)_4(CH_2OH)_2$, p-isononylphenoxypoly-(glycidol), decanoyl-N-methylglucamide, n-decyl β -D-glucopyranoside, n-decyl β -D-maltopyranoside, n-dodecyl β -D-glucopyranoside, n-dodecyl β -D-maltoside, heptanoyl-N-methylglucamide, n-heptyl- β -D-glucopyranoside, n-heptyl β -D-thioglucoside, n-hexyl β -D-glucopyranoside, nonanoyl-N-methylglucamide, n-nonyl β -D-glucopyranoside, octanoyl-N-methylglucamide, n-octyl- β -D-glucopyranoside, octyl β -D-thioglucopyranoside, lysozyme, PEG-phospholipid, PEG-cholesterol, PEG-vitamin A, PEG-vitamin E, and random copolymers of vinyl acetate and vinyl pyrrolidone.

57. (Previously Presented) The method of claim 55, wherein the surface stabilizer is selected from the group consisting of cationic lipids, polymethylmethacrylate trimethylammonium bromide, sulfonium compounds, polyvinylpyrrolidone-2-dimethylaminoethyl methacrylate dimethyl sulfate, hexadecyltrimethyl ammonium bromide, phosphonium compounds, quarternary ammonium compounds, benzyl-di(2-chloroethyl)ethylammonium bromide, coconut trimethyl ammonium chloride, coconut trimethyl ammonium bromide, coconut methyl dihydroxyethyl ammonium chloride, coconut methyl dihydroxyethyl ammonium bromide, decyl triethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride

bromide, C₁₂₋₁₅ dimethyl hydroxyethyl ammonium chloride, C₁₂₋₁₅dimethyl hydroxyethyl ammonium chloride bromide, coconut dimethyl hydroxyethyl ammonium chloride, coconut dimethyl hydroxyethyl ammonium bromide, myristyl trimethyl ammonium methyl sulphate, lauryl dimethyl benzyl ammonium chloride, lauryl dimethyl benzyl ammonium bromide, lauryl dimethyl (ethenoxy)₄ ammonium chloride, lauryl dimethyl (ethenoxy)₄ ammonium bromide, N-alkyl (C₁₂₋₁₈)dimethylbenzyl ammonium chloride, N-alkyl (C₁₄₋₁₈)dimethylbenzyl ammonium chloride, N-tetradecyldimethylbenzyl ammonium chloride monohydrate, dimethyl dodecyl ammonium chloride, N-alkyl and (C₁₂₋₁₄) dimethyl 1-naphthylmethyl ammonium chloride, trimethylammonium halide, alkyl-trimethylammonium salts, dialkyl-dimethylammonium salts, lauryl trimethyl ammonium chloride, ethoxylated alkyamidoalkyldialkylammonium salt, an ethoxylated trialkyl ammonium salt, dialkylbenzene dialkylammonium chloride, N-dodecyldimethyl ammonium chloride, N-tetradecyldimethylbenzyl ammonium, chloride monohydrate, N-alkyl(C₁₂₋₁₄) dimethyl 1-naphthylmethyl ammonium chloride, dodecyldimethylbenzyl ammonium chloride, dialkyl benzenealkyl ammonium chloride, lauryl trimethyl ammonium chloride, alkylbenzyl methyl ammonium chloride, alkyl benzyl dimethyl ammonium bromide, C₁₂ trimethyl ammonium bromides, C₁₅ trimethyl ammonium bromides, C₁₇ trimethyl ammonium bromides, dodecylbenzyl triethyl ammonium chloride, poly-diallyldimethylammonium chloride dimethyl ammonium chlorides, alkyldimethylammonium halogenides, tricetyl methyl ammonium chloride, decyltrimethylammonium bromide, dodecyltriethylammonium bromide, tetradecyltrimethylammonium bromide, methyl trioctylammonium chloride, polyquaternium 10, tetrabutylammonium bromide, benzyl trimethylammonium bromide, choline esters, benzalkonium chloride, stearylalkonium chloride compounds, cetyl pyridinium bromide, cetyl pyridinium chloride, halide salts of quaternized polyoxyethylalkylamines, quaternized ammonium salt polymers, alkyl pyridinium salts, amines, amine salts, amine oxides, imide azolinium salts, protonated quaternary acrylamides, methylated quaternary polymers, and cationic guar.

58. (Original) The method of claim 40, wherein the surface stabilizer is selected from the group consisting of hydroxypropylmethylcellulose (HPMC), docusate sodium, and a combination thereof.

59. (Previously Presented) The method of claim 40, wherein after preparation of a first nanoparticulate sildenafil free base composition, a second sildenafil free base composition having an effective average particle size of greater than 2 microns is combined with the first sildenafil free base composition.

60. (Original) The method of claim 40, wherein either prior or subsequent to preparation of the nanoparticulate sildenafil free base composition, at least one non-sildenafil free base active agent is added to the sildenafil free base composition.

61. (Previously Presented) The method of claim 60, wherein said non-sildenafil free base active agent is selected from the group consisting of alpha adrenergic receptor blocking agents, delaquamine, phenotolamine, doxazosin, prostaglandins, alprostadil, misoprostol, testosterone, antidepressants, trazodone, apomorphine, NO donors, and central nervous system stimulants.

62. (Previously Presented) The method of claim 60, wherein said non-sildenafil free base active agent is selected from the group consisting of non-sildenafil free base PDE5 inhibitors, amino acids, proteins, peptides, nucleotides, anti-obesity drugs, nutraceuticals, dietary supplements, carotenoids, central nervous system stimulants, corticosteroids, elastase inhibitors, anti-fungals, alkylxanthine, oncology therapies, anti-emetics, analgesics, opioids, antipyretics, cardiovascular agents, anti-inflammatory agents, anthelmintics, anti-arrhythmic agents, antibiotics, anticoagulants, antidepressants, antidiabetic agents, antiepileptics, antihistamines, antihypertensive agents, antimuscarinic agents, antimycobacterial agents, antineoplastic agents, immunosuppressants, antithyroid agents, antiviral agents, anxiolytics, sedatives, astringents, alpha-adrenergic receptor blocking agents, beta-adrenoceptor blocking agents, blood products, blood substitutes, cardiac inotropic agents, contrast media, corticosteroids, cough suppressants, diagnostic agents, diagnostic imaging agents, diuretics, dopaminergics, haemostatics, immunological agents, lipid regulating agents, muscle relaxants, parasympathomimetics, parathyroid hormones, calcitonin, bisphosphonates, prostaglandins, radio-pharmaceuticals, sex hormones, anti-allergic agents, stimulants, anoretics, sympathomimetics, thyroid agents, vasodilators, vasomodulator, xanthines, mu receptor antagonists, kappa receptor antagonists, non-narcotic analgesics, monoamine uptake

inhibitors, adenosine regulating agents, cannabinoid, Substance P antagonists, neurokinin-1 receptor antagonists, and sodium channel blockers.

63. (Original) The method of claim 62, wherein said nutraceutical is selected from the group consisting of yohimbine, *Cornus officinalis*, *Cinnamomum aromaticum*, *Panax ginseng* and *Pulsatilla pratensis*.

64. (Original) The method of claim 62, wherein the amino acid is L-arginine.

65. (Original) The method of claim 62, wherein said non-sildenafil free base PDE5 inhibitor active agent is selected from the group consisting of vardenafil, tadalafil, TA-1790, UK-114542, Compound 14, EMD221829, EMR 62 203, T-1032, M-54033, M-54018, and E-4010.

66. (Previously Presented) The method of any one of claims 60-65, wherein at least one non-sildenafil free base active agent has an effective average particle size of less than 2 microns.

67. (Previously Presented) The method of any one of claims 60-65, wherein at least one non-sildenafil free base active agent has an effective average particle size of greater than 2 microns.

68. (Currently Amended) A method ~~of treating a condition where a selective inhibiting PDE5 inhibitor is indicated~~, in a subject in need, comprising administering to the subject an effective amount of a composition comprising:

- (a) particles of sildenafil free base or a salt thereof having an effective average particle size of less than 2000 nm; and
 - (b) associated with the surface thereof at least one surface stabilizer,
- wherein the composition is bioequivalent when administered under fed and fasted conditions.

69. (Previously Presented) The method of claim 68, wherein upon administration the composition has an AUC that differs between the fed and fasted state by an amount

selected from the group consisting of, less than 25%, less than 20%, less than 15%, less than 10%, less than-5%, less than 3%, and less than 1%.

70. (Cancelled)

71. (Previously Presented) The method of claim 68, wherein upon administration the composition has a T_{\max} that differs between the fed and fasted state by an amount selected from the group consisting of less than 60%, less than 50%, less than 40%, less than 30%, less than 20%, less than 15%, less than 10%, less than 5%, and less than 3%.

72. (Cancelled)

73. (Previously Presented) The method of claim 68, wherein upon administration the composition has a C_{\max} that differs between the fed and fasted state by an amount selected from the group consisting of, less than 40%, less than 30%, less than 20%, less than 15%, less than 10%, less than 5%, and less than 3%.

74. (Previously Presented) The method of claim 68, wherein sildenafil free base is selected from the group consisting of a crystalline phase, an amorphous phase, a semi-crystalline phase, and mixtures thereof.

75. (Previously Presented) The method of claim 68, wherein the effective average particle size of the sildenafil free base particles is selected from the group consisting of less than 1900 nm, less than-1800 nm, less than 1700 nm, less than 1600 nm, less than 1500 nm, less than-1400 nm, less than 1300 nm, less than 200 nm, less than 1100 nm, less than-1000 nm, less than 900 nm, less than 800 nm, less than 700 nm, less than-600 nm, less than-500 nm, less than 400 nm, less than 300 nm, less than 250 nm, less than 200 nm, less than 100 nm, less than 75 nm, and less than-50 nm.

76. (Original) The method of claim 68, wherein the composition is formulated for an administration form selected from the group consisting of oral, pulmonary, rectal, ophthalmic, colonic, parenteral, intracisternal, intravaginal, intraperitoneal, local, buccal, nasal, and topical administration.

77. (Original) The method of claim 68, wherein the composition is a dosage form selected from the group consisting of liquid dispersions, gels, aerosols, ointments, creams, controlled release formulations, fast melt formulations, lyophilized formulations, tablets, capsules, delayed release formulations, extended release formulations, pulsatile release formulations, and mixed immediate release and controlled release formulations.

78. (Original) The method of claim 68, wherein the nanoparticulate sildenafil free base composition is formulated into an aerosol or nasal spray and has a T_{\max} which is less than that observed with a composition of non-nanoparticulate sildenafil.

79. (Original) The method of claim 68, wherein the composition further comprises one or more pharmaceutically acceptable excipients, carriers, or a combination thereof.

80. (Original) The method of claim 68, wherein sildenafil free base is present in an amount selected from the group consisting of from about 99% to about 0.001%, from about 95% to about 0.5%, and from about 90% to about 0.5%, by weight, based on the total combined dry weight of sildenafil free base and at least one surface stabilizer, not including other excipients.

81. (Original) The method of claim 68, wherein at least one surface stabilizer is present in an amount selected from the group consisting of from about 0.5% to about 99.999%, from about 5.0% to about 99.9%, or from about 10% to about 99.5%, by weight, based on the total combined dry weight of sildenafil free base and at least one surface stabilizer, not including other excipients.

82. (Original) The method of claim 68, wherein the sildenafil free base composition comprises at least two surface stabilizers.

83. (Original) The method of claim 68, wherein the surface stabilizer is selected from the group consisting of an anionic surface stabilizer, a cationic surface stabilizer, an ionic surface stabilizer, and a zwitterionic surface stabilizer.

84. (Previously Presented) The method of claim 83, wherein the at least one surface stabilizer is selected from the group consisting of cetyl pyridinium chloride, gelatin, casein, phosphatides, dextran, glycerol, gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glycerol monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers, polyoxyethylene castor oil, polyoxyethylene sorbitan fatty acid esters, polyethylene glycols, dodecyl trimethyl ammonium bromide, polyoxyethylene stearates, colloidal silicon dioxide, phosphates, sodium dodecylsulfate, carboxymethylcellulose calcium, hydroxypropyl celluloses, hydroxypropyl methylcellulose, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hydroxypropylmethyl-cellulose phthalate, noncrystalline cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol, polyvinylpyrrolidone, 4-(1,1,3,3-tetramethylbutyl)-phenol polymer with ethylene oxide and formaldehyde, poloxamers, poloxamines, a charged phospholipid, dioctylsulfosuccinate, dialkylesters of sodium sulfosuccinic acid, sodium lauryl sulfate, alkyl aryl polyether sulfonates, mixtures of sucrose stearate and sucrose distearate, $C_{18}H_{37}CH_2C(O)N(CH_3)-CH_2(CHOH)_4(CH_2OH)_2$, p-isononylphenoxypoly-(glycidol), decanoyl-N-methylglucamide, n-decyl β -D-glucopyranoside, n-decyl β -D-maltopyranoside, n-dodecyl β -D-glucopyranoside, n-dodecyl β -D-maltoside, heptanoyl-N-methylglucamide, n-heptyl- β -D-glucopyranoside, n-heptyl β -D-thioglucoside, n-hexyl β -D-glucopyranoside, nonanoyl-N-methylglucamide, n-nonyl β -D-glucopyranoside, octanoyl-N-methylglucamide, n-octyl- β -D-glucopyranoside, octyl β -D-thioglucopyranoside, lysozyme, PEG-phospholipid, PEG-cholesterol, PEG-vitamin A, PEG-vitamin E, and random copolymers of vinyl acetate and vinyl pyrrolidone.

85. (Previously Presented) The method of claim 83, wherein the surface stabilizer is selected from the group consisting of benzalkonium chloride, polymethylmethacrylate trimethylammonium bromide, polyvinylpyrrolidone-2-dimethylaminoethyl methacrylate dimethyl sulfate, hexadecyltrimethyl ammonium bromide, cationic lipids, sulfonium compounds, phosphonium compounds, quarternary ammonium compounds, benzyl-di(2-chloroethyl)ethylammonium bromide, coconut trimethyl ammonium chloride, coconut trimethyl ammonium bromide, coconut methyl dihydroxyethyl ammonium chloride, coconut

methyl dihydroxyethyl ammonium bromide, decyl triethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride bromide, C₁₂₋₁₅ dimethyl hydroxyethyl ammonium chloride, C₁₂₋₁₅ dimethyl hydroxyethyl ammonium chloride bromide, coconut dimethyl hydroxyethyl ammonium chloride, coconut dimethyl hydroxyethyl ammonium bromide, myristyl trimethyl ammonium methyl sulphate, lauryl dimethyl benzyl ammonium chloride, lauryl dimethyl benzyl ammonium bromide, lauryl dimethyl (ethenoxy)₄ ammonium chloride, lauryl dimethyl (ethenoxy)₄ ammonium bromide, N-alkyl (C₁₂₋₁₈) dimethylbenzyl ammonium chloride, N-alkyl (C₁₄₋₁₈) dimethylbenzyl ammonium chloride, N-tetradecyldimethylbenzyl ammonium chloride monohydrate, dimethyl dodecyl ammonium chloride, N-alkyl and (C₁₂₋₁₄) dimethyl 1-naphthylmethyl ammonium chloride, trimethylammonium halide, alkyl-trimethylammonium salts, dialkyl-dimethylammonium salts, lauryl trimethyl ammonium chloride, ethoxylated alkyamidoalkyldialkylammonium salt, an ethoxylated trialkyl ammonium salt, dialkylbenzene dialkylammonium chloride, N- dodecyldimethyl ammonium chloride, N-tetradecyldimethylbenzyl ammonium, chloride monohydrate, N-alkyl(C₁₂₋₁₄) dimethyl 1-naphthylmethyl ammonium chloride, dodecyldimethylbenzyl ammonium chloride, dialkyl benzenealkyl ammonium chloride, lauryl trimethyl ammonium chloride, alkylbenzyl methyl ammonium chloride, alkyl benzyl dimethyl ammonium bromide, C₁₂ trimethyl ammonium bromides, C₁₅ trimethyl ammonium bromides, C₁₇ trimethyl ammonium bromides, dodecylbenzyl triethyl ammonium chloride, poly-diallyldimethylammonium chloride dimethyl ammonium chlorides, alkyldimethylammonium halogenides, tricetyl methyl ammonium chloride, decyltrimethylammonium bromide, dodecyltriethylammonium bromide, tetradecyltrimethylammonium bromide, methyl trioctylammonium chloride, polyquaternium 10, tetrabutylammonium bromide, benzyl trimethylammonium bromide, choline esters, benzalkonium chloride, stearalkonium chloride compounds, cetyl pyridinium bromide, cetyl pyridinium chloride, halide salts of quaternized polyoxyethylalkylamines, quaternized ammonium salt polymers, alkyl pyridinium salts, amines, amine salts, amine oxides, imide azolinium salts, protonated quaternary acrylamides, methylated quaternary polymers, and cationic guar.

86. (Original) The method of claim 68, wherein the surface stabilizer is selected from the group consisting of hydroxypropylmethylcellulose (HPMC), docusate sodium, and a combination thereof.

87. (Previously Presented) The method of claim 68, additionally comprising administering at least one additional nanoparticulate sildenafil free base composition having an effective average particle size of less than 2 microns, wherein said additional nanoparticulate sildenafil free base composition has an effective average particle size which is different than the particle size of the nanoparticulate sildenafil free base composition of claim 68.

88. (Original) The method of claim 68, additionally comprising administering at least one non-sildenafil free base active agent.

89. (Previously Presented) The method of claim 88, wherein the active agent is selected from the group consisting of alpha adrenergic receptor blocking agents, delaquamine, phenotolamine, doxazosin, prostaglandins, alprostadil, misoprostol, testosterone, antidepressants, trazodone, apomorphine, NO donors, and central nervous system stimulants.

90. (Previously Presented) The method of claim 88, wherein said active agent is selected from the group consisting of non-sildenafil free base PDE5 inhibitors, amino acids, proteins, peptides, nucleotides, anti-obesity drugs, nutraceuticals, dietary supplements, central nervous symptom stimulants, carotenoids, corticosteroids, elastase inhibitors, anti-fungals, alkylxanthine, oncology therapies, anti-emetics, analgesics, opioids, antipyretics, cardiovascular agents, anti-inflammatory agents, anthelmintics, anti-arrhythmic agents, antibiotics, anticoagulants, antidepressants, antidiabetic agents, antiepileptics, antihistamines, antihypertensive agents, antimuscarinic agents, antimycobacterial agents, antineoplastic agents, immunosuppressants, antithyroid agents, antiviral agents, anxiolytics, sedatives, astringents, alpha-adrenergic receptor blocking agents, beta-adrenoceptor blocking agents, blood products, blood substitutes, cardiac inotropic agents, contrast media, corticosteroids, cough suppressants, diagnostic agents, diagnostic imaging agents, diuretics, dopaminergics, haemostatics, immunological agents, lipid regulating agents, muscle relaxants,

parasympathomimetics, parathyroid hormones, calcitonin, biphosphonates, prostaglandins, radio- pharmaceuticals, sex hormones, anti-allergic agents, stimulants, anoretics, sympathomimetics, thyroid agents, vasodilators, vasomodulator, xanthines, mu receptor antagonists, kappa receptor antagonists, non-narcotic analgesics, monoamine uptake inhibitors, adenosine regulating agents, cannabinoid, Substance P antagonists, neurokinin-1 receptor antagonists, and sodium channel blockers.

91. (Original) The method of claim 90, wherein the nutraceutical is selected from the group consisting of yohimbine, *Cornus officinalis*, *Cinnamomum aromaticum*, *Panax ginseng* and *Pulsatilla pratensis*.

92. (Original) The method of claim 90, wherein the amino acid is L-arginine.

93. (Previously Presented) The method of claim 90, wherein the non-sildenafil free base PDE5 inhibitor is selected from the group consisting of vardenafil, tadalafil, TA-1790, UK-114542, Compound 14, EMD221829, EMR 62 203, T-1032, M-54033, M-54018, and E-4010.

94. (Previously Presented) The method of any one of claims 88-93, wherein at least one non-sildenafil free base active agent has an effective average particle size of less than 2 microns.

95. (Previously Presented) The method of any one of claims 88-93, wherein at least one non-sildenafil free base active agent has an effective average particle size of greater than 2 microns.

96. (Previously Presented) The method of claim 68, wherein upon administration the composition has a T_{max} less than that of a composition of non-nanoparticulate sildenafil or a composition of nanoparticulate sildenafil citrate, administered at the same dosage.

97. (Previously Presented) The method of claim 68, wherein upon administration the composition has a C_{max} greater than the C_{max} of a composition of non-nanoparticulate

sildenafil or a composition of nanoparticulate sildenafil citrate, administered at the same dosage.

98. (Previously Presented) The method of claim 68, wherein upon administration the composition has an AUC greater than the AUC of a composition of non-nanoparticulate sildenafil or a composition of nanoparticulate sildenafil citrate, administered at the same dosage.

99. (Previously Presented) The method of claim 68, wherein upon administration the composition has a T_{\max} selected from the group consisting of less than 1.5 hours, less than 1.25 hours, less than 1.0 hours, less than 50 minutes, less than 40 minutes, less than 45 minutes, less than 35 minutes, less than 30 minutes, less than 25 minutes, less than 20 minutes, less than 15 minutes, and less than 10 minutes.

100. (Previously Presented) The method of claim 68, wherein administration of a 100 mg oral dose of the nanoparticulate sildenafil free base composition, in a healthy adult male, results in a mean C_{\max} of greater than 440 ng/mL, a T_{\max} of less than 60 minutes, or a combination thereof.

101. (Previously Presented) The method of claim 68, wherein administration of a 100 mg oral dose of the nanoparticulate sildenafil free base composition produces a C_{\max} which is selected from the group consisting of greater than 440 ng/mL, greater than 450 ng/mL, greater than 500 ng/mL, greater than 550 ng/mL, greater than 600 ng/mL, greater than 650 ng/mL, greater than 700 ng/mL, greater than 750 ng/mL, greater than 800 ng/mL, greater than 850 ng/mL, greater than 900 ng/mL, greater than 950 ng/mL, greater than 1000 ng/mL, greater than 1050 ng/mL, greater than 1100 ng/mL, greater than 1150 ng/mL, greater than 1200 ng/mL, greater than 1250 ng/mL, greater than 1300 ng/mL, greater than 1350 ng/mL, and greater than 1400 ng/mL.

102. (Cancelled)

103. (Previously Presented) The method of claim 68, wherein the condition is male erectile dysfunction.

104. (Previously Presented) The method of claim 68, wherein the condition is selected from the group consisting of impotence, female sexual dysfunction, clitoral dysfunction, female hypoactive sexual desire disorder, female sexual arousal disorder, female sexual pain disorder, female sexual orgasmic dysfunction, and sexual dysfunction due to spinal cord injury.

105. (Previously Presented) The method of claim 68, wherein the condition is selected from the group consisting of premature labor, dysmenorrhea, benign prostatic hyperplasia, bladder outlet obstruction, incontinence, stable angina, unstable angina, variant (Prinzmetal) angina, hypertension, pulmonary hypertension, chronic obstructive pulmonary disease, coronary artery disease, congestive heart failure, atherosclerosis, conditions of reduced blood vessel patency, peripheral vascular disease, stroke, nitrate induced tolerance, bronchitis, allergic asthma, chronic asthma, allergic rhinitis, glaucoma, diabetic gastroparesis, pre-eclampsia, Kawasaki's syndrome, nitrate tolerance, multiple sclerosis, diabetic nephropathy, peripheral diabetic neuropathy, Alzheimer's disease, acute respiratory failure, psoriasis, skin necrosis, cancer metastasis, baldness, nutcracker oesophagus, anal fissure, hemorrhoids, and hypoxic vasoconstriction.

106. (Previously Presented) The method of claim 68, wherein the condition is selected from the group consisting of diseases characterized by disorders of gut motility and irritable bowel syndrome.

107. (Original) The method of claim 68, wherein said subject is a human.

LISTING OF CLAIMS

1. – 16. (Cancelled)

17. (Previously Presented) A sterile filterable dispersion comprising:

(a) an aqueous dispersion medium;

(b) fluticasone particles sufficiently small to pass through a 0.2 μ m filter, and have a phase selected from the group consisting of a crystalline phase, an amorphous phase, and a semi-crystalline phase; and

(c) at least one surface stabilizer adsorbed on the surface of the fluticasone particles, wherein the dispersion is sterilized by filtration through a 0.2 μ m filter.

18. (Cancelled)

19. (Previously Presented) The sterile filterable fluticasone dispersion of claim 17, wherein the surface stabilizer is tyloxapol.

20. (Previously Presented) The sterile filterable fluticasone dispersion of claim 17, wherein at least 99.9% of the fluticasone particles have a particle size of less than 200 nm.

21. (Previously Presented) The sterile filterable fluticasone dispersion of claim 17, wherein at least 90% of the fluticasone particles have a particle size of less than 130 nm.

22. (Previously Presented) A sterile filterable fluticasone composition comprising:

(a) particles of fluticasone or a salt thereof, wherein at least 99.9% of the fluticasone particles have a particle size of less than 200 nm; and

(b) tyloxapol as a surface stabilizer,

wherein the composition is sterilized by filtration through a 0.2 μ m filter.

23. (Previously Presented) A nanoparticulate fluticasone composition comprising:

- (a) particles of fluticasone or a salt thereof, wherein the fluticasone particles have an effective average particle size of less than 150 nm; and
- (b) at least one surface stabilizer adsorbed on the surface of the fluticasone particles, wherein the composition is sterilized by filtration through a 0.2 μ m filter.

24. (Previously Presented) The composition of claim 23, wherein the effective average particle size of the fluticasone particles is selected from the group consisting of less than 140 nm, less than 130 nm, less than 120 nm, less than 110 nm, less than 100 nm, less than 90 nm, less than 80 nm, less than 70 nm, less than 60 nm, and less than 50 nm.

25.-26. (Cancelled)

27. (Original) The composition of claim 23 formulated for administration selected from the group consisting of oral, pulmonary, rectal, ophthalmic, colonic, parenteral, intracisternal, intravaginal, intraperitoneal, local, buccal, nasal, and topical administration.

28. (Original) The composition of claim 23 further comprising one or more pharmaceutically acceptable excipients, carriers, or a combination thereof.

29. (Previously Presented) The composition of claim 28, wherein the fluticasone particles are present in the composition in an amount selected from the group consisting of from 99.5% to 0.001%, from 95% to 0.1%, and from 90% to 0.5%, by weight, based on the total combined dry weight of the fluticasone and at least one surface stabilizer, not including other excipients.

30. (Previously Presented) The composition of claim 28, wherein the at least one surface stabilizer is present in an amount selected from the group consisting of from 0.5% to 99.999%, from 5.0% to 99.9%, and from 10% to 99.5%, by weight, based on the total combined dry weight of the fluticasone and at least one surface stabilizer, not including other excipients.

31. (Original) The composition of claim 23, comprising at least two surface stabilizers.

32. (Original) The composition of claim 23, wherein the surface stabilizer is selected from the group consisting of an anionic surface stabilizer, a cationic surface stabilizer, a zwitterionic surface stabilizer, and an ionic surface stabilizer.

33. (Previously Presented) The composition of claim 32, wherein the at least one surface stabilizer is selected from the group consisting of cetyl pyridinium chloride, gelatin, casein, phosphatides, dextran, glycerol, gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glycerol monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers, polyoxyethylene castor oils, polyoxyethylene sorbitan fatty acid esters, polyethylene glycols, dodecyl trimethyl ammonium bromide, polyoxyethylene stearates, colloidal silicon dioxide, phosphates, sodium dodecylsulfate, carboxymethylcellulose calcium, hydroxypropyl celluloses, hypromellose, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hypromellose phthalate, noncrystalline cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol, polyvinylpyrrolidone, 4-(1,1,3,3-tetramethylbutyl)-phenol polymer with ethylene oxide and formaldehyde, poloxamers; poloxamines, a charged phospholipid, dioctylsulfosuccinate, dialkylesters of sodium sulfosuccinic acid, sodium lauryl sulfate, alkyl aryl polyether sulfonates, mixtures of sucrose stearate and sucrose distearate, p-isononylphenoxypoly-(glycidol), decanoyl-N-methylglucamide; n-decyl β -D-glucopyranoside; n-decyl β -D-maltopyranoside; n-dodecyl β -D-glucopyranoside; n-dodecyl β -D-maltoside; heptanoyl-N-methylglucamide; n-heptyl- β -D-glucopyranoside; n-heptyl β -D-thioglucoside; n-hexyl β -D-glucopyranoside; nonanoyl-N-methylglucamide; n-noyl β -D-glucopyranoside; octanoyl-N-methylglucamide; n-octyl- β -D-glucopyranoside; octyl β -D-thioglucopyranoside; lysozyme, PEG-derivatized phospholipid, PEG-derivatized cholesterol, PEG-derivatized vitamin A, PEG-derivatized vitamin E, and random copolymers of vinyl acetate and vinyl pyrrolidone.

34. (Previously Presented) The composition of claim 32, wherein the at least one cationic surface stabilizer is selected from the group consisting of a polymer, a biopolymer, a polysaccharide, a cellulosic, an alginate, a nonpolymeric compound, a phospholipid, zwitterionic stabilizers, poly-n-methylpyridinium, anthryl pyridinium chloride, chitosan, polylysine, polyvinylimidazole, polybrene, polymethylmethacrylate trimethylammoniumbromide bromide (PMMTMABr), hexyldeyltrimethylammonium bromide (HDMAB), polyvinylpyrrolidone-2-dimethylaminoethyl methacrylate dimethyl sulfate, 1,2 Dipalmitoyl-sn-Glycero-3-Phosphoethanolamine-N-[Amino(Polyethylene Glycol)2000] (sodium salt), Poly(2-methacryloxyethyl trimethylammonium bromide), poloxamines, lysozyme, alginic acid, carrageenan, and nonionic, high molecular weight, water-soluble poly(ethylene oxide) polymers.

35. (Previously Presented) The composition of claim 32, wherein the at least one cationic surface stabilizer is selected from the group consisting of cationic lipids, sulfonium, phosphonium, quarternary ammonium compounds, stearyltrimethylammonium chloride, benzyl-di(2-chloroethyl)ethylammonium bromide, coconut trimethyl ammonium chloride, coconut trimethyl ammonium bromide, coconut methyl dihydroxyethyl ammonium chloride, coconut methyl dihydroxyethyl ammonium bromide, decyl triethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium bromide, C₁₂₋₁₅dimethyl hydroxyethyl ammonium chloride, C₁₂₋₁₅dimethyl hydroxyethyl ammonium bromide, coconut dimethyl hydroxyethyl ammonium chloride, coconut dimethyl hydroxyethyl ammonium bromide, myristyl trimethyl ammonium methyl sulphate, lauryl dimethyl benzyl ammonium chloride, lauryl dimethyl benzyl ammonium bromide, lauryl dimethyl (ethenoxy)₄ ammonium chloride, lauryl dimethyl (ethenoxy)₄ ammonium bromide, N-alkyl (C₁₂₋₁₈)dimethylbenzyl ammonium chloride, N-alkyl (C₁₄₋₁₈)dimethyl-benzyl ammonium chloride, N-tetradecylidmethylbenzyl ammonium chloride monohydrate, dimethyl didecyl ammonium chloride, N-alkyl and (C₁₂₋₁₄) dimethyl 1-naphthylmethyl ammonium chloride, trimethylammonium halide, alkyl-trimethylammonium salts, dialkyl-dimethylammonium salts, lauryl trimethyl ammonium chloride, ethoxylated alkyamidoalkyldialkylammonium salt, an

ethoxylated trialkyl ammonium salt, dialkylbenzene dialkylammonium chloride, N-didecyldimethyl ammonium chloride, N-tetradecyldimethylbenzyl ammonium, chloride monohydrate, N-alkyl(C₁₂₋₁₄) dimethyl 1-naphthylmethyl ammonium chloride, dodecyldimethylbenzyl ammonium chloride, dialkyl benzenealkyl ammonium chloride, lauryl trimethyl ammonium chloride, alkylbenzyl methyl ammonium chloride, alkyl benzyl dimethyl ammonium bromide, C₁₂, C₁₅, C₁₇ trimethyl ammonium bromides, dodecylbenzyl triethyl ammonium chloride, poly-diallyldimethylammonium chloride (DADMAC), dimethyl ammonium chlorides, alkyldimethylammonium halogenides, tricetyl methyl ammonium chloride, decyltrimethylammonium bromide, dodecyltriethylammonium bromide, tetradecyltrimethylammonium bromide, methyl trioctylammonium chloride, polyquaternium 10, tetrabutylammonium bromide, benzyl trimethylammonium bromide, choline esters, benzalkonium chloride, stearalkonium chloride compounds, cetyl pyridinium bromide, cetyl pyridinium chloride, halide salts of quaternized polyoxyethylalkylamines, quaternized ammonium salt polymers, imidazoline, alkyl pyridinium salts, amines, protonated quaternary acrylamides, methylated quaternary polymers, and cationic guar.

36. (Previously Presented) The composition of claim 35, wherein the amine is selected from the group consisting of alkylamines, dialkylamines, alkanolamines, polyethylenepolyamines, N,N-dialkylaminoalkyl acrylates, vinyl pyridine, amine salts, lauryl amine acetate, stearyl amine acetate, alkylpyridinium salt, alkylimidazolium salt, amine oxides, and imide azolinium salts.

37. (Original) The composition of claim 34, wherein the cationic surface stabilizer is a nonpolymeric compound selected from the group consisting of benzalkonium chloride, a carbonium compound, a phosphonium compound, an oxonium compound, a halonium compound, a cationic organometallic compound, a quaternary phosphorous compound, a pyridinium compound, an anilinium compound, an ammonium compound, a hydroxylammonium compound, a primary ammonium compound, a secondary ammonium compound, a tertiary

ammonium compound, behenalkonium chloride, benzethonium chloride, cetylpyridinium chloride, behentrimonium chloride, lauralkonium chloride, cetalkonium chloride, cetrimonium bromide, cetrimonium chloride, cethylamine hydrofluoride, chlorallylmethenamine chloride (Quaternium-15), distearyldimonium chloride (Quaternium-5), dodecyl dimethyl ethylbenzyl ammonium chloride(Quaternium-14), Quaternium-22, Quaternium-26, Quaternium-18 hectorite, dimethylaminoethylchloride hydrochloride, cysteine hydrochloride, diethanolammonium POE (10) oleyl ether phosphate, diethanolammonium POE (3)oleyl ether phosphate, tallow alkonium chloride, dimethyl dioctadecylammoniumbentonite, stearalkonium chloride, domiphen bromide, denatonium benzoate, myristalkonium chloride, laurtrimonium chloride, ethylenediamine dihydrochloride, guanidine hydrochloride, pyridoxine HCl, iofetamine hydrochloride, meglumine hydrochloride, methylbenzethonium chloride, myrtrimonium bromide, oleyltrimonium chloride, polyquaternium-1, procainehydrochloride, cocobetaine, stearalkonium bentonite, stearalkoniumhectonite, stearyl trihydroxyethyl propylenediamine dihydrofluoride, tallowtrimonium chloride, and hexadecyltrimethyl ammonium bromide.

38. (Original) The composition according to any of claims 32, 34, 35, 36, or 37, wherein the composition is bioadhesive.

39. (Previously Presented) A method of making a fluticasone composition comprising:

contacting fluticasone or a salt thereof with at least one surface stabilizer for a time and under conditions sufficient to provide a particulate fluticasone composition comprising-particles of fluticasone having an effective average particle size of less than 150 nm; and

passing the particulate fluticasone composition through a 0.2 μ m filter to sterilize the particulate fluticasone composition.

40. (Original) The method of claim 39, wherein said contacting comprises grinding.

41. (Original) The method of claim 40, wherein said grinding comprises wet grinding.

42. (Original) The method of claim 39, wherein said contacting comprises homogenizing.

43. (Original) The method of claim 39, wherein said contacting comprises:

- (a) dissolving the fluticasone particles in a solvent;
- (b) adding the resulting fluticasone solution to a solution comprising at least one surface stabilizer; and
- (c) precipitating the solubilized fluticasone having at least one surface stabilizer by the addition thereto of a non-solvent.

44. (Previously Presented) The method of claim 39, wherein the effective average particle size of the fluticasone particles is selected from the group consisting of less than 140 nm, less than 130 nm, less than 120 nm, less than 110 nm, less than 100 nm, less than 90 nm, less than 80 nm, less than 70 nm, less than 60 nm, and less than 50 nm.

45.-46. (Cancelled)

47. (Previously Presented) The method of claim 39, wherein the fluticasone has a phase selected from the group consisting of a crystalline phase, an amorphous phase, and a semi-crystalline phase.

48. (Previously Presented) The method of claim 39 further comprising formulating the particulate fluticasone composition into a dosage form suitable for administration to a patient, wherein the route of administration is selected from the group consisting of oral, pulmonary, rectal, ophthalmic, colonic, parenteral, intracisternal, intravaginal, intraperitoneal, local, buccal, nasal, and topical administration.

49. (Previously Presented) The method of claim 39, wherein the contacting step further comprises contacting the fluticasone with one or more pharmaceutically acceptable excipients, carriers, or a combination thereof.

50. (Previously Presented) The method of claim 49, wherein the fluticasone particles are present in the particulate fluticasone composition an amount selected from the group consisting of from 99.5% to 0.001%, from 95% to 0.1%, and from 90% to 0.5%, by weight, based on the total combined dry weight of the fluticasone particles and the at least one surface stabilizer, not including other excipients.

51. (Previously Presented) The method of claim 49, wherein the at least one surface stabilizer is present in the particulate fluticasone composition in an amount selected from the group consisting of from 0.5% to 99.999%, from 5.0% to 99.9%, and from 10% to 99.5%, by weight, based on the total combined dry weight of the fluticasone and the at least one surface stabilizer, not including other excipients.

52. (Original) The method of claim 39, wherein the fluticasone composition comprises at least two surface stabilizers.

53. (Original) The method of claim 39, wherein the surface stabilizer is selected from the group consisting of an anionic surface stabilizer, a cationic surface stabilizer, a zwitterionic surface stabilizer, and an ionic surface stabilizer.

54. (Previously Presented) The method of claim 53, wherein the at least one surface stabilizer is selected from the group consisting of cetyl pyridinium chloride, gelatin, casein, phosphatides, dextran, glycerol, gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glycerol monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers, polyoxyethylene castor oils, polyoxyethylene sorbitan fatty acid esters, polyethylene glycols, dodecyl trimethyl ammonium bromide, polyoxyethylene stearates, colloidal silicon dioxide, phosphates, sodium dodecylsulfate,

carboxymethylcellulose calcium, hydroxypropyl celluloses, hypromellose, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hypromellose phthalate, noncrystalline cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol, polyvinylpyrrolidone, 4-(1,1,3,3-tetramethylbutyl)-phenol polymer with ethylene oxide and formaldehyde, poloxamers; poloxamines, a charged phospholipid, dioctylsulfosuccinate, dialkylesters of sodium sulfosuccinic acid, sodium lauryl sulfate, alkyl aryl polyether sulfonates, mixtures of sucrose stearate and sucrose distearate, p-isononylphenoxypoly-(glycidol), decanoyl-N-methylglucamide; n-decyl β -D-glucopyranoside; n-decyl β -D-maltopyranoside; n-dodecyl β -D-glucopyranoside; n-dodecyl β -D-maltoside; heptanoyl-N-methylglucamide; n-heptyl- β -D-glucopyranoside; n-heptyl β -D-thioglucoside; n-hexyl β -D-glucopyranoside; nonanoyl-N-methylglucamide; n-noyl β -D-glucopyranoside; octanoyl-N-methylglucamide; n-octyl- β -D-glucopyranoside; octyl β -D-thioglucopyranoside; lysozyme, PEG-derivatized phospholipid, PEG-derivatized cholesterol, PEG-derivatized vitamin A, PEG-derivatized vitamin E, and random copolymers of vinyl acetate and vinyl pyrrolidone.

55. (Previously Presented) The method of claim 53, wherein the at least one cationic surface stabilizer is selected from the group consisting of a polymer, a biopolymer, a polysaccharide, a cellulosic, an alginate, a nonpolymeric compound, a phospholipid, zwitterionic stabilizers, poly-n-methylpyridinium, anthryl pyridinium chloride, chitosan, polylysine, polyvinylimidazole, polybrene, polymethylmethacrylate trimethylammoniumbromide bromide (PMMTMABr), hexyldeyltrimethylammonium bromide (HDMAB), polyvinylpyrrolidone-2-dimethylaminoethyl methacrylate dimethyl sulfate, 1,2 Dipalmitoyl-sn-Glycero-3-Phosphoethanolamine-N-[Amino(Polyethylene Glycol)2000] (sodium salt), Poly(2-methacryloxyethyl trimethylammonium bromide), poloxamines, lysozyme, alginic acid, carrageenan, and nonionic, high molecular weight, water-soluble poly(ethylene oxide) polymers.

56. (Previously Presented) The method of claim 53, wherein the at least one cationic surface stabilizer is selected from the group consisting of cationic lipids, sulfonium,

phosphonium, quarternary ammonium compounds, stearyltrimethylammonium chloride, benzyl-di(2-chloroethyl)ethylammonium bromide, coconut trimethyl ammonium chloride, coconut trimethyl ammonium bromide, coconut methyl dihydroxyethyl ammonium chloride, coconut methyl dihydroxyethyl ammonium bromide, decyl triethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium bromide, C₁₂₋₁₅dimethyl hydroxyethyl ammonium chloride, C₁₂₋₁₅dimethyl hydroxyethyl ammonium bromide, coconut dimethyl hydroxyethyl ammonium chloride, coconut dimethyl hydroxyethyl ammonium bromide, myristyl trimethyl ammonium methyl sulphate, lauryl dimethyl benzyl ammonium chloride, lauryl dimethyl benzyl ammonium bromide, lauryl dimethyl (ethenoxy)₄ ammonium chloride, lauryl dimethyl (ethenoxy)₄ ammonium bromide, N-alkyl (C₁₂₋₁₈)dimethylbenzyl ammonium chloride, N-alkyl (C₁₄₋₁₈)dimethyl-benzyl ammonium chloride, N-tetradecyldimethylbenzyl ammonium chloride monohydrate, dimethyl didecyl ammonium chloride, N-alkyl and (C₁₂₋₁₄) dimethyl 1-naphthylmethyl ammonium chloride, trimethylammonium halide, alkyl-trimethylammonium salts, dialkyl-dimethylammonium salts, lauryl trimethyl ammonium chloride, ethoxylated alkyamidoalkyldialkylammonium salt, an ethoxylated trialkyl ammonium salt, dialkylbenzene dialkylammonium chloride, N-didecyldimethyl ammonium chloride, N-tetradecyldimethylbenzyl ammonium, chloride monohydrate, N-alkyl(C₁₂₋₁₄) dimethyl 1-naphthylmethyl ammonium chloride, dodecyldimethylbenzyl ammonium chloride, dialkyl benzenealkyl ammonium chloride, lauryl trimethyl ammonium chloride, alkylbenzyl methyl ammonium chloride, alkyl benzyl dimethyl ammonium bromide, C₁₂, C₁₅, C₁₇ trimethyl ammonium bromides, dodecylbenzyl triethyl ammonium chloride, poly-diallyldimethylammonium chloride (DADMAC), dimethyl ammonium chlorides, alkyl dimethylammonium halogenides, tricetyl methyl ammonium chloride, decyltrimethylammonium bromide, dodecyltriethylammonium bromide, tetradecyltrimethylammonium bromide, methyl trioctylammonium chloride, polyquaternium 10, tetrabutylammonium bromide, benzyl trimethylammonium bromide, choline esters, benzalkonium chloride, stearalkonium chloride compounds, cetyl pyridinium bromide, cetyl

pyridinium chloride, halide salts of quaternized polyoxyethylalkylamines quaternized ammonium salt polymers, imidazoline, alkyl pyridinium salts, amines, protonated quaternary acrylamides, methylated quaternary polymers, and cationic guar.

57. (Previously Presented) The method of claim 56, wherein the amine is selected from the group consisting of alkylamines, dialkylamines, alkanolamines, polyethylenepolyamines, N,N-dialkylaminoalkyl acrylates, vinyl pyridine, amine salts, lauryl amine acetate, stearyl amine acetate, alkylpyridinium salt, alkylimidazolium salt, amine oxides, and imide azolinium salts.

58. (Original) The method of claim 55, wherein the cationic surface stabilizer is a nonpolymeric compound selected from the group consisting of benzalkonium chloride, a carbonium compound, a phosphonium compound, an oxonium compound, a halonium compound, a cationic organometallic compound, a quaternary phosphorous compound, a pyridinium compound, an anilinium compound, an ammonium compound, a hydroxylammonium compound, a primary ammonium compound, a secondary ammonium compound, a tertiary ammonium compound, behenalkonium chloride, benzethonium chloride, cetylpyridinium chloride, behentrimonium chloride, lauralkonium chloride, cetalkonium chloride, cetrimonium bromide, cetrimonium chloride, cethylamine hydrofluoride, chlorallylmethenamine chloride (Quaternium-15), distearyldimonium chloride (Quaternium-5), dodecyl dimethyl ethylbenzyl ammonium chloride(Quaternium-14), Quaternium-22, Quaternium-26, Quaternium-18 hectorite, dimethylaminoethylchloride hydrochloride, cysteine hydrochloride, diethanolammonium POE (10) oleyl ether phosphate, diethanolammonium POE (3)oleyl ether phosphate, tallow alkonium chloride, dimethyl dioctadecylammoniumbentonite, stearalkonium chloride, domiphen bromide, denatonium benzoate, myristalkonium chloride, laurtrimonium chloride, ethylenediamine dihydrochloride, guanidine hydrochloride, pyridoxine HCl, iofetamine hydrochloride, meglumine hydrochloride, methylbenzethonium chloride, myrtrimonium bromide, oleyltrimonium chloride, polyquaternium-1, procainehydrochloride, cocobetaine, stearalkonium bentonite,

stearalkoniumhectonite, stearyl trihydroxyethyl propylenediamine dihydrofluoride, tallowtrimonium chloride, and hexadecyltrimethyl ammonium bromide.

59. (Original) The method according to any of claims 53, 55, 56, 57, or 58, wherein the fluticasone composition is bioadhesive.

60. (Previously Presented) A method of treating a subject in need of either symptomatic or prophylactic treatment with a sterile particulate fluticasone composition comprising the step of administering to the subject an effective amount of the sterile particulate fluticasone composition sterilized by passing the composition through a 0.2 μ m filter, wherein the sterile particulate fluticasone composition comprises particles of fluticasone or a salt thereof and at least one surface stabilizer, wherein the fluticasone particles have an effective average particle size of less than 150 nm.

61. (Previously Presented) The method of claim 60, wherein the effective average particle size of the fluticasone particles is selected from the group consisting of less than 140 nm, less than 130 nm, less than 120 nm, less than 110 nm, less than 100 nm, less than 90 nm, less than 80 nm, less than 70 nm, less than 60 nm, and less than 50 nm.

62.-63. (Cancelled)

64. (Previously Presented) The method of claim 60, wherein the subject has a condition selected from the group consisting of a respiratory related illness, inflammatory airways diseases, obstructive airways diseases, Whipple's disease, AIDS related pneumonia, asthma, emphysema, respiratory distress syndrome, chronic obstructive pulmonary disease, chronic bronchitis, cystic fibrosis, pneumonia, acquired immune deficiency syndrome related respiratory disorders, seasonal rhinitis, perennial rhinitis, seasonal allergic rhinitis, seasonal nonallergic rhinitis, perennial allergic rhinitis, perennial nonallergic rhinitis, and skin conditions treatable with topical corticosteroids.

65. (Original) The method of claim 64, wherein the subject has a condition selected from the group consisting of intrinsic (non-allergic) asthma, extrinsic (allergic) asthma, wheezy-infant syndrome, acute lung injury, acute respiratory distress syndrome, chronic obstructive pulmonary disease, chronic obstructive airways disease, chronic obstructive lung disease, chronic bronchitis, emphysema, bronchiectasis, exacerbation of airways hyperreactivity consequent to other drug therapy, and pneumoconiosis.

66. (Previously Presented) The method of claim 60, wherein the prophylactic efficacy of the treatment is evidenced by one or more characteristics selected from the group consisting of reduced frequency of symptomatic attack, reduced severity of symptomatic attack, improvement in lung function, improved airways hyperreactivity, and a reduced requirement for other symptomatic therapy.

67. (Original) The method of claim 60, wherein the subject is a human.

68. (Cancelled)

69. (Previously Presented) The method of claim 60, wherein the fluticasone has a phase selected from the group consisting of a crystalline phase, an amorphous phase and a semi-crystalline phase.

70. (Previously Presented) The method of claim 60, wherein the sterile particulate fluticasone composition is formulated into a dosage form suitable for administration to a patient, wherein said route of administration is selected from the group consisting of oral, pulmonary, rectal, ophthalmic, colonic, parenteral, intracisternal, intravaginal, intraperitoneal, local, buccal, nasal, and topical administration.

71. (Original) The method of claim 60, wherein the fluticasone composition further comprises one or more pharmaceutically acceptable excipients, carriers, or a combination thereof.

72. (Previously Presented) The method of claim 71, wherein the particulate fluticasone is present in the sterile particulate fluticasone composition in an amount selected from the group consisting of from 99.5% to 0.001%, from 95% to 0.1%, and from 90% to 0.5%, by weight, based on the total combined dry weight of the fluticasone and at least one surface stabilizer, not including other excipients.

73. (Previously Presented) The method of claim 71, wherein the at least one surface stabilizer is present in the sterile particulate fluticasone composition in an amount selected from the group consisting of from 0.5% to 99.999%, from 5.0% to 99.9%, and from 10% to 99.5%, by weight, based on the total combined dry weight of the fluticasone and at least one surface stabilizer, not including other excipients.

74. (Previously Presented) The method of claim 60, wherein the sterile particulate fluticasone composition comprises at least two surface stabilizers.

75. (Original) The method of claim 60, wherein the surface stabilizer is selected from the group consisting of an anionic surface stabilizer, a cationic surface stabilizer, a zwitterionic surface stabilizer, and an ionic surface stabilizer.

76. (Previously Presented) The method of claim 75, wherein the at least one surface stabilizer is selected from the group consisting of cetyl pyridinium chloride, gelatin, casein, phosphatides, dextran, glycerol, gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glycerol monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers, polyoxyethylene castor oils, polyoxyethylene sorbitan fatty acid esters, polyethylene glycols, dodecyl trimethyl ammonium bromide, polyoxyethylene stearates, colloidal silicon dioxide, phosphates, sodium dodecylsulfate, carboxymethylcellulose calcium, hydroxypropyl celluloses, hypromellose, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hypromellose phthalate, noncrystalline cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol,

polyvinylpyrrolidone, 4-(1,1,3,3-tetramethylbutyl)-phenol polymer with ethylene oxide and formaldehyde, poloxamers; poloxamines, a charged phospholipid, dioctylsulfosuccinate, dialkylesters of sodium sulfosuccinic acid, sodium lauryl sulfate, alkyl aryl polyether sulfonates, mixtures of sucrose stearate and sucrose distearate, p-isononylphenoxypoly-(glycidol), decanoyl-N-methylglucamide; n-decyl β -D-glucopyranoside; n-decyl β -D-maltopyranoside; n-dodecyl β -D-glucopyranoside; n-dodecyl β -D-maltoside; heptanoyl-N-methylglucamide; n-heptyl- β -D-glucopyranoside; n-heptyl β -D-thioglucoside; n-hexyl β -D-glucopyranoside; nonanoyl-N-methylglucamide; n-nonyl β -D-glucopyranoside; octanoyl-N-methylglucamide; n-octyl- β -D-glucopyranoside; octyl β -D-thioglucopyranoside; lysozyme, PEG-derivatized phospholipid, PEG-derivatized cholesterol, PEG-derivatized vitamin A, PEG-derivatized vitamin E, and random copolymers of vinyl acetate and vinyl pyrrolidone.

77. (Previously Presented) The method of claim 75, wherein the at least one cationic surface stabilizer is selected from the group consisting of a polymer, a biopolymer, a polysaccharide, a cellulosic, an alginate, a nonpolymeric compound, a phospholipid, zwitterionic stabilizers, poly-n-methylpyridinium, anthryl pyridinium chloride, chitosan, polylysine, polyvinylimidazole, polybrene, polymethylmethacrylate trimethylammoniumbromide bromide (PMMTMABr), hexyldesyltrimethylammonium bromide (HDMAB), polyvinylpyrrolidone-2-dimethylaminoethyl methacrylate dimethyl sulfate, 1,2 Dipalmitoyl-sn-Glycero-3-Phosphoethanolamine-N-[Amino(Polyethylene Glycol)2000] (sodium salt), Poly(2-methacryloxyethyl trimethylammonium bromide), poloxamines, lysozyme, alginic acid, carrageenan, and nonionic, high molecular weight, watersoluble poly(ethylene oxide) polymers.

78. (Previously Presented) The method of claim 75, wherein the at least one cationic surface stabilizer is selected from the group consisting of cationic lipids, sulfonium, phosphonium, quarternary ammonium compounds, stearyltrimethylammonium chloride, benzyl-di(2-chloroethyl)ethylammonium bromide, coconut trimethyl ammonium chloride, coconut trimethyl ammonium bromide, coconut methyl dihydroxyethyl ammonium chloride, coconut

methyl dihydroxyethyl ammonium bromide, decyl triethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium bromide, C₁₂₋₁₅dimethyl hydroxyethyl ammonium chloride, C₁₂₋₁₅dimethyl hydroxyethyl ammonium bromide, coconut dimethyl hydroxyethyl ammonium chloride, coconut dimethyl hydroxyethyl ammonium bromide, myristyl trimethyl ammonium methyl sulphate, lauryl dimethyl benzyl ammonium chloride, lauryl dimethyl benzyl ammonium bromide, lauryl dimethyl (ethenoxy)₄ ammonium chloride, lauryl dimethyl (ethenoxy)₄ ammonium bromide, N-alkyl (C₁₂₋₁₈)dimethylbenzyl ammonium chloride, N-alkyl (C₁₄₋₁₈)dimethyl-benzyl ammonium chloride, N-tetradecyldimethylbenzyl ammonium chloride monohydrate, dimethyl didecyl ammonium chloride, N-alkyl and (C₁₂₋₁₄) dimethyl 1-naphthylmethyl ammonium chloride, trimethylammonium halide, alkyl-trimethylammonium salts, dialkyl-dimethylammonium salts, lauryl trimethyl ammonium chloride, ethoxylated alkyamidoalkyldialkylammonium salt, an ethoxylated trialkyl ammonium salt, dialkylbenzene dialkylammonium chloride, N-didecyldimethyl ammonium chloride, N-tetradecyldimethylbenzyl ammonium, chloride monohydrate, N-alkyl(C₁₂₋₁₄) dimethyl 1-naphthylmethyl ammonium chloride, dodecyldimethylbenzyl ammonium chloride, dialkyl benzenealkyl ammonium chloride, lauryl trimethyl ammonium chloride, alkylbenzyl methyl ammonium chloride, alkyl benzyl dimethyl ammonium bromide, C₁₂, C₁₅, C₁₇ trimethyl ammonium bromides, dodecylbenzyl triethyl ammonium chloride, poly-diallyldimethylammonium chloride (DADMAC), dimethyl ammonium chlorides, alkyldimethylammonium halogenides, tricetyl methyl ammonium chloride, decyltrimethylammonium bromide, dodecyltriethylammonium bromide, tetradecyltrimethylammonium bromide, methyl trioctylammonium chloride, polyquaternium 10, tetrabutylammonium bromide, benzyl trimethylammonium bromide, choline esters, benzalkonium chloride, stearalkonium chloride compounds, cetyl pyridinium bromide, cetyl pyridinium chloride, halide salts of quaternized polyoxyethylalkylamines, quaternized ammonium salt polymers, imidazoline, alkyl pyridinium salts, amines, protonated quaternary acrylamides, methylated quaternary polymers, and cationic guar.

79. (Previously Presented) The method of claim 78, wherein the amine is selected from the group consisting of alkylamines, dialkylamines, alkanolamines, polyethylenepolyamines, N,N-dialkylaminoalkyl acrylates, vinyl pyridine, amine salts, lauryl amine acetate, stearyl amine acetate, alkylpyridinium salt, alkylimidazolium salt, amine oxides, and imide azolinium salts.

80. (Original) The method of claim 77, wherein the cationic surface stabilizer is a nonpolymeric compound selected from the group consisting of benzalkonium chloride, a carbonium compound, a phosphonium compound, an oxonium compound, a halonium compound, a cationic organometallic compound, a quaternary phosphorous compound, a pyridinium compound, an anilinium compound, an ammonium compound, a hydroxylammonium compound, a primary ammonium compound, a secondary ammonium compound, a tertiary ammonium compound, behenalkonium chloride, benzethonium chloride, cetylpyridinium chloride, behentrimonium chloride, lauralkonium chloride, cetalkonium chloride, cetrimonium bromide, cetrimonium chloride, cethylamine hydrofluoride, chlorallylmethenamine chloride (Quaternium-15), distearyldimonium chloride (Quaternium-5), dodecyl dimethyl ethylbenzyl ammonium chloride(Quaternium-14), Quaternium-22, Quaternium-26, Quaternium-18 hectorite, dimethylaminoethylchloride hydrochloride, cysteine hydrochloride, diethanolammonium POE (10) oleyl ether phosphate, diethanolammonium POE (3)oleyl ether phosphate, tallow alkonium chloride, dimethyl dioctadecylammoniumbentonite, stearalkonium chloride, domiphen bromide, denatonium benzoate, myristalkonium chloride, laurtrimonium chloride, ethylenediamine dihydrochloride, guanidine hydrochloride, pyridoxine HCl, iofetamine hydrochloride, meglumine hydrochloride, methylbenzethonium chloride, myrtrimonium bromide, oleyltrimonium chloride, polyquaternium-1, procainehydrochloride, cocobetaine, stearalkonium bentonite, stearalkoniumhectonite, stearyl trihydroxyethyl propylenediamine dihydrofluoride, tallowtrimonium chloride, and hexadecyltrimethyl ammonium bromide.

81. (Original) The method according to any of claims 75, 77, 78, 79, or 80, wherein the composition is bioadhesive.

82.-99. (Cancelled)

LISTING OF CLAIMS

1. (Previously Presented) A composition comprising:
 - (a) particles of glipizide or a salt thereof, wherein the glipizide particles have an effective average particle size of less than about 2000 nm; and
 - (b) at least one surface stabilizer;wherein the glipizide or a salt thereof is present in an amount of from about 99.5% to about 0.001%, by weight, based on the total combined weight of the glipizide or a salt thereof and at least one surface stabilizer, not including other excipients; and
wherein the at least one surface stabilizer is present in an amount of from about 0.5% to about 99.999% by weight, based on the total combined dry weight of the glipizide or a salt thereof and at least one surface stabilizer, not including other excipients.
2. (Previously Presented) The composition of claim 1, wherein the glipizide is selected from the group consisting of a crystalline phase, an amorphous phase, and a semi-crystalline phase.
3. (Original) The composition of claim 1, wherein the effective average particle size of the glipizide particles is selected from the group consisting of less than about 1900 nm, less than about 1800 nm, less than about 1700 nm, less than about 1600 nm, less than about 1500 nm, less than about 1400 nm, less than about 1300 nm, less than about 1200 nm, less than about 1100 nm, less than about 1000 nm, less than about 900 nm, less than about 800 nm, less than about 700 nm, less than about 600 nm, less than about 500 nm, less than about 400 nm, less than about 300 nm, less than about 250 nm, less than about 200 nm, less than about 100 nm, less than about 75 nm, and less than about 50 nm.
4. (Previously Presented) The composition of claim 1, wherein the composition is formulated for administration selected from the group consisting of oral, pulmonary, rectal,

ophthalmic, colonic, parenteral, intracisternal, intravaginal, intraperitoneal, local, buccal, nasal, and topical administration.

5. (Original) The composition of claim 1 formulated into a dosage form selected from the group consisting of liquid dispersions, oral suspensions, gels, aerosols, ointments, creams, controlled release formulations, fast melt formulations, lyophilized formulations, tablets, capsules, delayed release formulations, extended release formulations, pulsatile release formulations, and mixed immediate release and controlled release formulations.

6. (Original) The composition of claim 1, wherein the composition further comprises one or more pharmaceutically acceptable excipients, carriers, or a combination thereof.

7. (Previously Presented) The composition of claim 1, wherein the glipizide or a salt thereof is present in an amount selected from the group consisting of from about 95% to about 0.1%, and from about 90% to about 0.5%, by weight, based on the total combined weight of the glipizide or a salt thereof and at least one surface stabilizer, not including other excipients.

8. (Previously Presented) The composition of claim 1, wherein the at least one surface stabilizer is present in an amount selected from the group consisting of from about 5.0% to about 99.9% by weight, and from about 10% to about 99.5% by weight, based on the total combined dry weight of the glipizide or a salt thereof and at least one surface stabilizer, not including other excipients.

9. (Original) The composition of claim 1, comprising at least two surface stabilizers.

10. (Original) The composition of claim 1, wherein the surface stabilizer is selected from the group consisting of an anionic surface stabilizer, a cationic surface stabilizer, a zwitterionic surface stabilizer, and an ionic surface stabilizer.

11. (Original) The composition of claim 10, wherein the at least one surface stabilizer is selected from the group consisting of cetyl pyridinium chloride, gelatin, casein, phosphatides, dextran, glycerol, gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glycerol monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers, polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters, polyethylene glycols, dodecyl trimethyl ammonium bromide, polyoxyethylene stearates, colloidal silicon dioxide, phosphates, sodium dodecylsulfate, carboxymethylcellulose calcium, hydroxypropyl celluloses, hypromellose, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hypromellose phthalate, noncrystalline cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol, polyvinylpyrrolidone, 4-(1,1,3,3-tetramethylbutyl)-phenol polymer with ethylene oxide and formaldehyde, poloxamers; poloxamines, a charged phospholipid, dioctylsulfosuccinate, dialkylesters of sodium sulfosuccinic acid, sodium lauryl sulfate, alkyl aryl polyether sulfonates, mixtures of sucrose stearate and sucrose distearate, p-isononylphenoxypoly-(glycidol), decanoyl-N-methylglucamide; n-decyl -D-glucopyranoside; n-decyl -D-maltopyranoside; n-dodecyl -D-glucopyranoside; n-dodecyl -D-maltoside; heptanoyl-N-methylglucamide; n-heptyl--D-glucopyranoside; n-heptyl -D-thioglucoside; n-hexyl -D-glucopyranoside; nonanoyl-N-methylglucamide; n-noyl -D-glucopyranoside; octanoyl-N-methylglucamide; n-octyl--D-glucopyranoside; octyl -D-thioglucopyranoside; lysozyme, PEG-phospholipid, PEG-cholesterol, PEG-cholesterol derivative, PEG-vitamin A, and random copolymers of vinyl acetate and vinyl pyrrolidone.

12. (Original) The composition of claim 10, wherein the at least one cationic surface stabilizer is selected from the group consisting of a polymer, a biopolymer, a polysaccharide, a cellulosic, an alginate, a nonpolymeric compound, and a phospholipid.

13. (Previously Presented) The composition of claim 10, wherein the surface stabilizer is selected from the group consisting of cationic lipids, polymethylmethacrylate

trimethylammonium bromide, sulfonium compounds, polyvinylpyrrolidone-2-dimethylaminoethyl methacrylate dimethyl sulfate, hexadecyltrimethyl ammonium bromide, phosphonium compounds, quarternary ammonium compounds, benzyl-di(2-chloroethyl)ethylammonium bromide, coconut trimethyl ammonium chloride, coconut trimethyl ammonium bromide, coconut methyl dihydroxyethyl ammonium chloride, coconut methyl dihydroxyethyl ammonium bromide, decyl triethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride bromide, C₁₂₋₁₅dimethyl hydroxyethyl ammonium chloride, C₁₂₋₁₅dimethyl hydroxyethyl ammonium chloride bromide, coconut dimethyl hydroxyethyl ammonium chloride, coconut dimethyl hydroxyethyl ammonium bromide, myristyl trimethyl ammonium methyl sulphate, lauryl dimethyl benzyl ammonium chloride, lauryl dimethyl benzyl ammonium bromide, lauryl dimethyl (ethenoxy)₄ ammonium chloride, lauryl dimethyl (ethenoxy)₄ ammonium bromide, N-alkyl (C₁₂₋₁₈)dimethylbenzyl ammonium chloride, N-alkyl (C₁₄₋₁₈)dimethyl-benzyl ammonium chloride, N-tetradecyldimethylbenzyl ammonium chloride monohydrate, dimethyl didecyl ammonium chloride, N-alkyl and (C₁₂₋₁₄) dimethyl 1-naphthylmethyl ammonium chloride, trimethylammonium halide, alkyl-trimethylammonium salts, dialkyl-dimethylammonium salts, lauryl trimethyl ammonium chloride, ethoxylated alkyamidoalkyldialkylammonium salt, an ethoxylated trialkyl ammonium salt, dialkylbenzene dialkylammonium chloride, N-didecyldimethyl ammonium chloride, N-tetradecyldimethylbenzyl ammonium, chloride monohydrate, N-alkyl(C₁₂₋₁₄) dimethyl 1-naphthylmethyl ammonium chloride, dodecyldimethylbenzyl ammonium chloride, dialkyl benzenealkyl ammonium chloride, lauryl trimethyl ammonium chloride, alkylbenzyl methyl ammonium chloride, alkyl benzyl dimethyl ammonium bromide, C₁₂ trimethyl ammonium bromides, C₁₅ trimethyl ammonium bromides, C₁₇ trimethyl ammonium bromides, dodecylbenzyl triethyl ammonium chloride, poly-diallyldimethylammonium chloride dimethyl ammonium chlorides, alkyl dimethylammonium halogenides, tricetyl methyl ammonium chloride, decyltrimethylammonium bromide,

dodecyltriethylammonium bromide, tetradecyltrimethylammonium bromide, methyl trioctylammonium chloride, tetrabutylammonium bromide, benzyl trimethylammonium bromide, choline esters, benzalkonium chloride, stearylalkonium chloride compounds, cetyl pyridinium bromide, cetyl pyridinium chloride, halide salts of quaternized polyoxyethylalkylamines, alkyl pyridinium salts; amines, amine salts, amine oxides, imide azolinium salts, protonated quaternary acrylamides, methylated quaternary polymers, and cationic guar.

14. (Original) The composition of any of claims 10, 12, or 13, wherein the composition is bioadhesive.

15. (Original) The composition of claim 1, comprising as a surface stabilizer hydroxypropyl cellulose.

16. (Previously Presented) A composition comprising:

- (a) particles of glipizide or a salt thereof, wherein the glipizide particles have an effective average particle size of less than about 2000 nm;
- (b) at least one surface stabilizer, and
- (c) at least one additional glipizide composition having an effective average particle size which is different from the effective average particle size of the glipizide particles of (a).

17. (Original) The composition of claim 1, additionally comprising one or more non-glipizide active agents.

18. (Original) The composition of claim 17, wherein said additionally one or more non-glipizide active agents are selected from the group consisting of nutraceuticals, amino acids, proteins, peptides, nucleotides, anti-obesity drugs, central nervous system stimulants, carotenoids, corticosteroids, elastase inhibitors, anti-fungals, oncology therapies, anti-emetics, analgesics, cardiovascular agents, anti-inflammatory agents, anthelmintics, anti-arrhythmic agents, antibiotics, anticoagulants, antidepressants, antidiabetic agents, antiepileptics, antihistamines, antihypertensive agents, antimuscarinic agents, antimycobacterial agents,

antineoplastic agents, immunosuppressants, antithyroid agents, antiviral agents, anxiolytics, sedatives, astringents, alpha-adrenergic receptor blocking agents, beta-adrenoceptor blocking agents, blood products, blood substitutes, cardiac inotropic agents, contrast media, corticosteroids, cough suppressants, diagnostic agents, diagnostic imaging agents, diuretics, dopaminergics, haemostatics, immunological agents, lipid regulating agents, muscle relaxants, parasympathomimetics, parathyroid calcitonin, parathyroid biphosphonates, prostaglandins, radio-pharmaceuticals, sex hormones, anti-allergic agents, stimulants, anoretics, sympathomimetics, thyroid agents, vasodilators, and xanthines.

19. (Original) The composition of claim 17, wherein said additionally one or more non-glipizide active agents are selected from the group consisting of acyclovir, alprazolam, altretamine, amiloride, amiodarone, benztropine mesylate, bupropion, cabergoline, candesartan, cerivastatin, chlorpromazine, ciprofloxacin, cisapride, clarithromycin, clonidine, clopidogrel, cyclobenzaprine, cyproheptadine, delavirdine, desmopressin, diltiazem, dipyridamole, dolasetron, enalapril maleate, enalaprilat, famotidine, felodipine, furazolidone, glipizide, irbesartan, ketoconazole, lansoprazole, loratadine, loxapine, mebendazole, mercaptopurine, milrinone lactate, minocycline, mitoxantrone, nelfinavir mesylate, nimodipine, norfloxacin, olanzapine, omeprazole, penciclovir, pimozide, tacolimus, quazepam, raloxifene, rifabutin, rifampin, risperidone, rizatriptan, saquinavir, sertraline, sildenafil, acetyl-sulfisoxazole, temazepam, thiabendazole, thioguanine, trandolapril, triamterene, trimetrexate, troglitazone, trovafloxacin, verapamil, vinblastine sulfate, mycophenolate, atovaquone, atovaquone, proguanil, ceftazidime, cefuroxime, etoposide, terbinafine, thalidomide, fluconazole, amsacrine, dacarbazine, teniposide, and acetylsalicylate.

20. (Original) The composition of claim 1, wherein upon administration to a mammal the glipizide particles redisperse such that the particles have an effective average particle size of less than about 2 microns.

21. (Original) The composition of claim 20, wherein upon administration the composition redisperses such that the glipizide particles have an effective average particle size selected from the group consisting of less than about 1900 nm, less than about 1800 nm, less than about 1700 nm, less than about 1600 nm, less than about 1500 nm, less than about 1400 nm, less than about 1300 nm, less than about 1200 nm, less than about 1100 nm, less than about 1000 nm, less than about 900 nm, less than about 800 nm, less than about 700 nm, less than about 600 nm, less than about 500 nm, less than about 400 nm, less than about 300 nm, less than about 250 nm, less than about 200 nm, less than about 150 nm, less than about 100 nm, less than about 75 nm, and less than about 50 nm.

22. (Original) The composition of claim 1, wherein the composition redisperses in a biorelevant media such that the glipizide particles have an effective average particle size of less than about 2 microns.

23. (Original) The composition of claim 22, wherein the biorelevant media is selected from the group consisting of water, aqueous electrolyte solutions, aqueous solutions of a salt, aqueous solutions of an acid, aqueous solutions of a base, and combinations thereof.

24. (Original) The composition of claim 22, wherein the composition redisperses in a biorelevant media such that the glipizide particles have an effective average particle size selected from the group consisting of less than about 1900 nm, less than about 1800 nm, less than about 1700 nm, less than about 1600 nm, less than about 1500 nm, less than about 1400 nm, less than about 1300 nm, less than about 1200 nm, less than about 1100 nm, less than about 1000 nm, less than about 900 nm, less than about 800 nm, less than about 700 nm, less than about 600 nm, less than about 500 nm, less than about 400 nm, less than about 300 nm, less than about 250 nm, less than about 200 nm, less than about 150 nm, less than about 100 nm, less than about 75 nm, and less than about 50 nm.

25.-35. (Cancelled)

36. (Original) The composition of claim 1 formulated into a liquid dosage form, wherein the dosage form has a viscosity of less than about 2000 mPa·s, measured at 20C, at a shear rate of 0.1 (1/s).

37. (Original) The composition of claim 36, having a viscosity at a shear rate of 0.1 (1/s), measured at 20C, selected from the group consisting of from about 2000 mPa·s to about 1 mPa·s, from about 1900 mPa·s to about 1 mPa·s, from about 1800 mPa·s to about 1 mPa·s, from about 1700 mPa·s to about 1 mPa·s, from about 1600 mPa·s to about 1 mPa·s, from about 1500 mPa·s to about 1 mPa·s, from about 1400 mPa·s to about 1 mPa·s, from about 1300 mPa·s to about 1 mPa·s, from about 1200 mPa·s to about 1 mPa·s, from about 1100 mPa·s to about 1 mPa·s, from about 1000 mPa·s to about 1 mPa·s, from about 900 mPa·s to about 1 mPa·s, from about 800 mPa·s to about 1 mPa·s, from about 700 mPa·s to about 1 mPa·s, from about 600 mPa·s to about 1 mPa·s, from about 500 mPa·s to about 1 mPa·s, from about 400 mPa·s to about 1 mPa·s, from about 300 mPa·s to about 1 mPa·s, from about 200 mPa·s to about 1 mPa·s, from about 175 mPa·s to about 1 mPa·s, from about 150 mPa·s to about 1 mPa·s, from about 125 mPa·s to about 1 mPa·s, from about 100 mPa·s to about 1 mPa·s, from about 75 mPa·s to about 1 mPa·s, from about 50 mPa·s to about 1 mPa·s, from about 25 mPa·s to about 1 mPa·s, from about 15 mPa·s to about 1 mPa·s, from about 10 mPa·s to about 1 mPa·s, and from about 5 mPa·s to about 1 mPa·s.

38. (Original) The composition of claim 36, wherein the viscosity of the dosage form is selected from the group consisting of less than about 1/200, less than about 1/100, less than about 1/50, less than about 1/25, and less than about 1/10 of the viscosity of a liquid dosage form of a non-nanoparticulate composition of glipizide, at about the same concentration per ml of glipizide.

39. (Original) The composition of claim 36, wherein the viscosity of the dosage form is selected from the group consisting of less than about 5%, less than about 10%, less than about 15%, less than about 20%, less than about 25%, less than about 30%, less than about 35%, less

than about 40%, less than about 45%, less than about 50%, less than about 55%, less than about 60%, less than about 65%, less than about 70%, less than about 75%, less than about 80%, less than about 85%, and less than about 90% of the viscosity of a liquid dosage form of a non-nanoparticulate composition of the glipizide, at about the same concentration per ml of glipizide.

40. (Previously Presented) A method of making a glipizide composition comprising contacting particles of glipizide or a salt thereof with at least one surface stabilizer for a time and under conditions sufficient to provide a glipizide composition having an effective average particle size of less than about 2000 nm;

wherein the glipizide or a salt thereof is present in an amount of from about 99.5% to about 0.001%, by weight, based on the total combined weight of the glipizide or a salt thereof and at least one surface stabilizer, not including other excipients; and

wherein the at least one surface stabilizer is present in an amount of from about 0.5% to about 99.999% by weight, based on the total combined dry weight of the glipizide or a salt thereof and at least one surface stabilizer, not including other excipients.

41. (Original) The method of claim 40, wherein said contacting comprises grinding.

42. (Original) The method of claim 41, wherein said grinding comprises wet grinding.

43. (Original) The method of claim 40, wherein said contacting comprises homogenizing.

44. (Previously Presented) The method of claim 40, wherein said contacting comprises:

- (a) dissolving the particles of a glipizide or a salt thereof in a solvent;
- (b) adding the resulting glipizide solution to a solution comprising at least one surface stabilizer; and

(c) precipitating the solubilized glipizide having at least one surface stabilizer adsorbed on the surface thereof by the addition thereto of a non-solvent.

45. (Previously Presented) The method of claim 40, wherein the glipizide or a salt thereof is selected from the group consisting of a crystalline phase, an amorphous phase, and a semi-crystalline phase.

46. (Original) The method of claim 40, wherein the effective average particle size of the glipizide particles is selected from the group consisting of less than about 1900 nm, less than about 1800 nm, less than about 1700 nm, less than about 1600 nm, less than about 1500 nm, less than about 1000 nm, less than about 1400 nm, less than about 1300 nm, less than about 1200 nm, less than about 1100 nm, less than about 900 nm, less than about 800 nm, less than about 700 nm, less than about 600 nm, less than about 500 nm, less than about 400 nm, less than about 300 nm, less than about 250 nm, less than about 200 nm, less than about 100 nm, less than about 75 nm, and less than about 50 nm.

47. (Previously Presented) The method of claim 40, wherein the composition is formulated for administration selected from the group consisting of oral, pulmonary, rectal, ophthalmic, colonic, parenteral, intracisternal, intravaginal, intraperitoneal, local, buccal, nasal, and topical administration.

48. (Original) The method of claim 40, wherein the composition further comprises one or more pharmaceutically acceptable excipients, carriers, or a combination thereof.

49. (Previously Presented) The method of claim 40, wherein the glipizide or a salt thereof is present in an amount selected from the group consisting of from about 95% to about 0.1%, and from about 90% to about 0.5%, by weight, based on the total combined weight of the glipizide or a salt thereof and at least one surface stabilizer, not including other excipients.

50. (Previously Presented) The method of claim 40, wherein the at least one surface stabilizer is present in an amount selected from the group consisting of from about 5.0% to about 99.9%, and from about 10% to about 99.5% by weight, based on the total combined dry weight of the glipizide or a salt thereof and at least one surface stabilizer, not including other excipients.

51. (Original) The method of claim 40, utilizing at least two surface stabilizers.

52. (Original) The method of claim 40, wherein the surface stabilizer is selected from the group consisting of an anionic surface stabilizer, a cationic surface stabilizer, a zwitterionic surface stabilizer, and an ionic surface stabilizer.

53. (Original) The method of claim 52, wherein the at least one surface stabilizer is selected from the group consisting of cetyl pyridinium chloride, gelatin, casein, phosphatides, dextran, glycerol, gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glycerol monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers, polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters, polyethylene glycols, dodecyl trimethyl ammonium bromide, polyoxyethylene stearates, colloidal silicon dioxide, phosphates, sodium dodecylsulfate, carboxymethylcellulose calcium, hydroxypropyl celluloses, hypromellose, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hypromellose phthalate, noncrystalline cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol, polyvinylpyrrolidone, 4-(1,1,3,3-tetramethylbutyl)-phenol polymer with ethylene oxide and formaldehyde, poloxamers; poloxamines, a charged phospholipid, dioctylsulfosuccinate, dialkylesters of sodium sulfosuccinic acid, sodium lauryl sulfate, alkyl aryl polyether sulfonates, mixtures of sucrose stearate and sucrose distearate, p-isononylphenoxypoly-(glycidol), decanoyl-N-methylglucamide; n-decyl -D-glucopyranoside; n-decyl -D-maltopyranoside; n-dodecyl -D-glucopyranoside; n-dodecyl -D-maltoside; heptanoyl-N-methylglucamide; n-heptyl--D-glucopyranoside; n-heptyl -D-thiogluconoside; n-hexyl -D-glucopyranoside; nonanoyl-N-methylglucamide; n-nonyl -D-glucopyranoside; octanoyl-N-methylglucamide; n-octyl--D-

glucopyranoside; octyl -D-thioglucopyranoside; lysozyme, PEG-phospholipid, PEG-cholesterol, PEG-cholesterol derivative, PEG-vitamin A, PEG-vitamin E, and random copolymers of vinyl acetate and vinyl pyrrolidone.

54. (Original) The method of claim 52, wherein the at least one cationic surface stabilizer is selected from the group consisting of a polymer, a biopolymer, a polysaccharide, a cellulosic, an alginate, a nonpolymeric compound, and a phospholipid.

55. (Previously Presented) The method of claim 52, wherein the surface stabilizer is selected from the group consisting of cationic lipids, polymethylmethacrylate trimethylammonium bromide, sulfonium compounds, polyvinylpyrrolidone-2-dimethylaminoethyl methacrylate dimethyl sulfate, hexadecyltrimethyl ammonium bromide, phosphonium compounds, quarternary ammonium compounds, benzyl-di(2-chloroethyl)ethylammonium bromide, coconut trimethyl ammonium chloride, coconut trimethyl ammonium bromide, coconut methyl dihydroxyethyl ammonium chloride, coconut methyl dihydroxyethyl ammonium bromide, decyl triethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride bromide, C₁₂₋₁₅ dimethyl hydroxyethyl ammonium chloride, C₁₂₋₁₅ dimethyl hydroxyethyl ammonium chloride bromide, coconut dimethyl hydroxyethyl ammonium chloride, coconut dimethyl hydroxyethyl ammonium bromide, myristyl trimethyl ammonium methyl sulphate, lauryl dimethyl benzyl ammonium chloride, lauryl dimethyl benzyl ammonium bromide, lauryl dimethyl (ethenoxy)₄ ammonium chloride, lauryl dimethyl (ethenoxy)₄ ammonium bromide, N-alkyl (C₁₂₋₁₈)dimethylbenzyl ammonium chloride, N-alkyl (C₁₄₋₁₈)dimethyl-benzyl ammonium chloride, N-tetradecylidmethylbenzyl ammonium chloride monohydrate, dimethyl didecyl ammonium chloride, N-alkyl and (C₁₂₋₁₄) dimethyl 1-naphthylmethyl ammonium chloride, trimethylammonium halide, alkyl-trimethylammonium salts, dialkyl-dimethylammonium salts, lauryl trimethyl ammonium chloride, ethoxylated alkyamidoalkyldialkylammonium salt, an ethoxylated trialkyl ammonium salt, dialkylbenzene dialkylammonium chloride, N-

didecyldimethyl ammonium chloride, N-tetradecyldimethylbenzyl ammonium, chloride monohydrate, N-alkyl(C₁₂₋₁₄) dimethyl 1-naphthylmethyl ammonium chloride, dodecyldimethylbenzyl ammonium chloride, dialkyl benzenealkyl ammonium chloride, lauryl trimethyl ammonium chloride, alkylbenzyl methyl ammonium chloride, alkyl benzyl dimethyl ammonium bromide, C₁₂ trimethyl ammonium bromides, C₁₅ trimethyl ammonium bromides, C₁₇ trimethyl ammonium bromides, dodecylbenzyl triethyl ammonium chloride, poly-diallyldimethylammonium chloride dimethyl ammonium chlorides, alkyldimethylammonium halogenides, tricetyl methyl ammonium chloride, decyltrimethylammonium bromide, dodecyltriethylammonium bromide, tetradecyltrimethylammonium bromide, methyl trioctylammonium chloride, tetrabutylammonium bromide, benzyl trimethylammonium bromide, choline esters, benzalkonium chloride, stearylalkonium chloride compounds, cetyl pyridinium bromide, cetyl pyridinium chloride, halide salts of quaternized polyoxyethylalkylamines, alkyl pyridinium salts; amines, amine salts, amine oxides, imide azolinium salts, protonated quaternary acrylamides, methylated quaternary polymers, and cationic guar.

56. (Original) The method of any of claims 52, 54, or 55, wherein the composition is bioadhesive.

57. (Original) The method of claim 40, utilizing hydroxypropylcellulose as a surface stabilizer.

58. (Previously Presented) A method of treating diabetes in a subject in need thereof comprising administering to the subject an effective amount of a composition comprising:

- (a) particles of a glipizide or a salt thereof, wherein the glipizide particles have an effective average particle size of less than about 2000 nm; and
- (b) at least one surface stabilizer,

wherein the glipizide or a salt thereof is present in an amount of from about 99.5% to about 0.001%, by weight, based on the total combined weight of the glipizide or a salt thereof and at least one surface stabilizer, not including other excipients;

wherein the at least one surface stabilizer is present in an amount of from about 0.5% to about 99.999% by weight, based on the total combined dry weight of the glipizide or a salt thereof and at least one surface stabilizer, not including other excipients.

59. (Previously Presented) The method of claim 58, wherein the glipizide or a salt thereof is selected from the group consisting of a crystalline phase, an amorphous phase, and a semi-crystalline phase.

60. (Original) The method of claim 58, wherein the effective average particle size of the glipizide particles is selected from the group consisting of less than about 1900 nm, less than about 1800 nm, less than about 1700 nm, less than about 1600 nm, less than about 1500 nm, less than about 1400 nm, less than about 1300 nm, less than about 1200 nm, less than about 1100 nm, less than about 1000 nm, less than about 900 nm, less than about 800 nm, less than about 700 nm, less than about 600 nm, less than about 500 nm, less than about 400 nm, less than about 300 nm, less than about 250 nm, less than about 200 nm, less than about 100 nm, less than about 75 nm, and less than about 50 nm.

61. (Previously Presented) The method of claim 58, wherein the composition is formulated for administration selected from the group consisting of oral, pulmonary, rectal, ophthalmic, colonic, parenteral, intracisternal, intravaginal, intraperitoneal, local, buccal, nasal, and topical administration.

62. (Original) The method of claim 58, wherein the composition is a dosage form selected from the group consisting of liquid dispersions, oral suspensions, gels, aerosols, ointments, creams, controlled release formulations, fast melt formulations, lyophilized

formulations, tablets, capsules, delayed release formulations, extended release formulations, pulsatile release formulations, and mixed immediate release and controlled release formulations.

63. (Original) The method of claim 58, wherein the composition further comprises one or more pharmaceutically acceptable excipients, carriers, or a combination thereof.

64. (Previously Presented) The method of claim 58, wherein the glipizide or a salt thereof is present in an amount selected from the group consisting of from about 95% to about 0.1% and from about 90% to about 0.5%, by weight, based on the total combined weight of the glipizide or a salt thereof and at least one surface stabilizer, not including other excipients.

65. (Previously Presented) The method of claim 58, wherein the at least one surface stabilizer is present in an amount selected from the group consisting of from about 5.0% to about 99.9%, and from about 10% to about 99.5% by weight, based on the total combined dry weight of the glipizide or a salt thereof and at least one surface stabilizer, not including other excipients.

66. (Original) The method of claim 58, utilizing at least two surface stabilizers.

67. (Original) The method of claim 58, wherein the surface stabilizer is selected from the group consisting of an anionic surface stabilizer, a cationic surface stabilizer, a zwitterionic surface stabilizer, and an ionic surface stabilizer.

68. (Original) The method of claim 67, wherein the at least one surface stabilizer is selected from the group consisting of cetyl pyridinium chloride, gelatin, casein, phosphatides, dextran, glycerol, gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glycerol monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers, polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters, polyethylene glycols, dodecyl trimethyl ammonium bromide, polyoxyethylene stearates, colloidal silicon dioxide, phosphates, sodium dodecylsulfate, carboxymethylcellulose calcium, hydroxypropyl celluloses, hypromellose,

carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hypromellose phthalate, noncrystalline cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol, polyvinylpyrrolidone, 4-(1,1,3,3-tetramethylbutyl)-phenol polymer with ethylene oxide and formaldehyde, poloxamers; poloxamines, a charged phospholipid, dioctylsulfosuccinate, dialkylesters of sodium sulfosuccinic acid, sodium lauryl sulfate, alkyl aryl polyether sulfonates, mixtures of sucrose stearate and sucrose distearate, p-isononylphenoxypoly-(glycidol), decanoyl-N-methylglucamide; n-decyl -D-glucopyranoside; n-decyl -D-maltopyranoside; n-dodecyl -D-glucopyranoside; n-dodecyl -D-maltoside; heptanoyl-N-methylglucamide; n-heptyl--D-glucopyranoside; n-heptyl -D-thioglucoside; n-hexyl -D-glucopyranoside; nonanoyl-N-methylglucamide; n-nonyl -D-glucopyranoside; octanoyl-N-methylglucamide; n-octyl--D-glucopyranoside; octyl -D-thioglucopyranoside; lysozyme, PEG-phospholipid, PEG-cholesterol, PEG-cholesterol derivative, PEG-vitamin A, PEG-vitamin E, and random copolymers of vinyl acetate and vinyl pyrrolidone.

69. (Original) The method of claim 67, wherein the at least one cationic surface stabilizer is selected from the group consisting of a polymer, a biopolymer, a polysaccharide, a cellulosic, an alginate, a nonpolymeric compound, and a phospholipid.

70. (Previously Presented) The method of claim 67, wherein the surface stabilizer is selected from the group consisting of benzalkonium chloride, polymethylmethacrylate trimethylammonium bromide, polyvinylpyrrolidone-2-dimethylaminoethyl methacrylate dimethyl sulfate, hexadecyltrimethyl ammonium bromide, cationic lipids, sulfonium compounds, phosphonium compounds, quarternary ammonium compounds, benzyl-di(2-chloroethyl)ethylammonium bromide, coconut trimethyl ammonium chloride, coconut trimethyl ammonium bromide, coconut methyl dihydroxyethyl ammonium chloride, coconut methyl dihydroxyethyl ammonium bromide, decyl triethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride bromide, C₁₂₋₁₅dimethyl hydroxyethyl ammonium chloride, C₁₂₋₁₅dimethyl hydroxyethyl ammonium

chloride bromide, coconut dimethyl hydroxyethyl ammonium chloride, coconut dimethyl hydroxyethyl ammonium bromide, myristyl trimethyl ammonium methyl sulphate, lauryl dimethyl benzyl ammonium chloride, lauryl dimethyl benzyl ammonium bromide, lauryl dimethyl (ethenoxy)₄ ammonium chloride, lauryl dimethyl (ethenoxy)₄ ammonium bromide, N-alkyl (C₁₂₋₁₈)dimethylbenzyl ammonium chloride, N-alkyl (C₁₄₋₁₈)dimethyl-benzyl ammonium chloride, N-tetradecyldimethylbenzyl ammonium chloride monohydrate, dimethyl didecyl ammonium chloride, N-alkyl and (C₁₂₋₁₄) dimethyl 1-naphthylmethyl ammonium chloride, trimethylammonium halide, alkyl-trimethylammonium salts, dialkyl-dimethylammonium salts, lauryl trimethyl ammonium chloride, ethoxylated alkyamidoalkyldialkylammonium salt, an ethoxylated trialkyl ammonium salt, dialkylbenzene dialkylammonium chloride, N-didecyldimethyl ammonium chloride, N-tetradecyldimethylbenzyl ammonium, chloride monohydrate, N-alkyl(C₁₂₋₁₄) dimethyl 1-naphthylmethyl ammonium chloride, dodecyldimethylbenzyl ammonium chloride, dialkyl benzenealkyl ammonium chloride, lauryl trimethyl ammonium chloride, alkylbenzyl methyl ammonium chloride, alkyl benzyl dimethyl ammonium bromide, C₁₂ trimethyl ammonium bromides, C₁₅ trimethyl ammonium bromides, C₁₇ trimethyl ammonium bromides, dodecylbenzyl triethyl ammonium chloride, poly-diallyldimethylammonium chloride dimethyl ammonium chlorides, alkyldimethylammonium halogenides, tricetyl methyl ammonium chloride, decyltrimethylammonium bromide, dodecyltriethylammonium bromide, tetradecyltrimethylammonium bromide, methyl trioctylammonium chloride, tetrabutylammonium bromide, benzyl trimethylammonium bromide, choline esters, benzalkonium chloride, stearalkonium chloride compounds, cetyl pyridinium bromide, cetyl pyridinium chloride, halide salts of quaternized polyoxyethylalkylamines, alkyl pyridinium salts; amines, amine salts, amine oxides, imide azolinium salts, protonated quaternary acrylamides, methylated quaternary polymers, and cationic guar.

71. (Original) The method of any of claims 67, 69, or 70, wherein the composition is bioadhesive.

72. (Original) The method of claim 58, utilizing hydroxypropylcellulose as a surface stabilizer.

73. (Original) The method of claim 58, additionally comprising administering one or more non-glipizide active agents.

74. (Original) The method of claim 73, wherein said additionally one or more non-glipizide active agents are selected from the group consisting of nutraceuticals, amino acids, proteins, peptides, nucleotides, anti-obesity drugs, central nervous system stimulants, carotenoids, corticosteroids, elastase inhibitors, anti-fungals, oncology therapies, anti-emetics, analgesics, cardiovascular agents, anti-inflammatory agents, anthelmintics, anti-arrhythmic agents, antibiotics, anticoagulants, antidepressants, antidiabetic agents, antiepileptics, antihistamines, antihypertensive agents, antimuscarinic agents, antimycobacterial agents, antineoplastic agents, immunosuppressants, antithyroid agents, antiviral agents, anxiolytics, sedatives, astringents, alpha-adrenergic receptor blocking agents, beta-adrenoceptor blocking agents, blood products, blood substitutes, cardiac inotropic agents, contrast media, corticosteroids, cough suppressants, diagnostic agents, diagnostic imaging agents, diuretics, dopaminergics, haemostatics, immunological agents, lipid regulating agents, muscle relaxants, parasympathomimetics, parathyroid calcitonin, parathyroid biphosphonates, prostaglandins, radio-pharmaceuticals, sex hormones, anti-allergic agents, stimulants, anoretics, sympathomimetics, thyroid agents, vasodilators, and xanthines.

75. (Original) The method of claim 73, wherein said additionally one or more non-glipizide active agents are selected from the group consisting of acyclovir, alprazolam, altretamine, amiloride, amiodarone, benztropine mesylate, bupropion, cabergoline, candesartan, cerivastatin, chlorpromazine, ciprofloxacin, cisapride, clarithromycin, clonidine, clopidogrel, cyclobenzaprine, cyproheptadine, delavirdine, desmopressin, diltiazem, dipyridamole, dolasetron, enalapril maleate, enalaprilat, famotidine, felodipine, furazolidone, glipizide, irbesartan, ketoconazole, lansoprazole, loratadine, loxapine, mebendazole, mercaptopurine, milrinone

lactate, minocycline, mitoxantrone, nelfinavir mesylate, nimodipine, norfloxacin, olanzapine, omeprazole, penciclovir, pimozide, tacolimus, quazepam, raloxifene, rifabutin, rifampin, risperidone, rizatriptan, saquinavir, sertraline, sildenafil, acetyl-sulfisoxazole, temazepam, thiabendazole, thioguanine, trandolapril, triamterene, trimetrexate, troglitazone, trovafloxacin, verapamil, vinblastine sulfate, mycophenolate, atovaquone, atovaquone, proguanil, ceftazidime, cefuroxime, etoposide, terbinafine, thalidomide, fluconazole, amsacrine, dacarbazine, teniposide, and acetylsalicylate.

76.-86. (Cancelled)

87. (Original) The method of claim 58, wherein the subject is a human.

88. (Original) The method of claim 58, wherein the method is used to treat indications where blood-glucose lowering drugs are typically used.

89. (Original) The method of claim 58, wherein the method is used to treat diabetes.

90. (Previously Presented) The method of claim 89, wherein the diabetes is non-insulin dependent diabetes mellitus.

LISTING OF CLAIMS

1. (Previously Presented) A nimesulide composition comprising:
 - (a) particles of nimesulide or a salt thereof, wherein the particles have an effective average particle size of less than 2000 nm; and
 - (b) at least one surface stabilizer adsorbed on the surface of the nimesulide particles.
2. (Previously Presented) The composition of claim 1, wherein the nimesulide is selected from the group consisting of a crystalline phase, an amorphous phase, and a semi-crystalline phase.
3. (Previously Presented) The composition of claim 1, wherein the effective average particle size of the nimesulide particles is selected from the group consisting of less than 1900 nm, less than 1800 nm, less than 1700 nm, less than 1600 nm, less than 1500 nm, less than 1400 nm, less than 1300 nm, less than 1200 nm, less than 1100 nm, less than 1000 nm, less than 900 nm, less than 800 nm, less than 700 nm, less than 600 nm, less than 500 nm, less than 400 nm, less than 300 nm, less than 250 nm, less than 200 nm, less than 100 nm, less than 75 nm, and less than 50 nm.
4. (Original) The composition of claim 1, wherein the composition is formulated for administration selected from the group consisting of oral, pulmonary, rectal, ophthalmic, colonic, parenteral, intracisternal, intravaginal, intraperitoneal, local, buccal, nasal, and topical administration.
5. (Original) The composition of claim 1 formulated into a dosage form selected from the group consisting of liquid dispersions, oral suspensions, gels, aerosols, ointments, creams, controlled release formulations, fast melt formulations, lyophilized formulations, tablets, capsules, delayed release formulations, extended release formulations, pulsatile release formulations, and mixed immediate release and controlled release formulations.

6. (Original) The composition of claim 1, wherein the composition further comprises one or more pharmaceutically acceptable excipients, carriers, or a combination thereof.

7. (Original) The composition of claim 1, wherein the nimesulide or a salt thereof is present in an amount selected from the group consisting of from about 99.5% to about 0.001%, from about 95% to about 0.1%, and from about 90% to about 0.5%, by weight, based on the total combined dry weight of the nimesulide or a salt thereof and at least one surface stabilizer, not including other excipients.

8. (Original) The composition of claim 1, wherein the at least one surface stabilizer is present in an amount selected from the group consisting of from about 0.5% to about 99.999% by weight, from about 5.0% to about 99.9% by weight, and from about 10% to about 99.5% by weight, based on the total combined dry weight of the nimesulide or a salt thereof and at least one surface stabilizer, not including other excipients.

9. (Original) The composition of claim 1, comprising two or more surface stabilizers.

10. (Previously Presented) The composition of claim 1, wherein the surface stabilizer is selected from the group consisting of an anionic surface stabilizer, a cationic surface stabilizer, a zwitterionic surface stabilizer, a non-ionic surface stabilizer, and an ionic surface stabilizer.

11. (Original) The composition of claim 10, wherein the at least one surface stabilizer is selected from the group consisting of cetyl pyridinium chloride, gelatin, casein, phosphatides, dextran, glycerol, gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glycerol monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers, polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters, polyethylene glycols, dodecyl trimethyl ammonium bromide, polyoxyethylene stearates, colloidal silicon dioxide, phosphates, sodium dodecylsulfate,

carboxymethylcellulose calcium, hydroxypropyl celluloses, hypromellose, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hypromellose phthalate, noncrystalline cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol, polyvinylpyrrolidone, 4-(1,1,3,3-tetramethylbutyl)-phenol polymer with ethylene oxide and formaldehyde, poloxamers; poloxamines, a charged phospholipid, dioctylsulfosuccinate, dialkylesters of sodium sulfosuccinic acid, sodium lauryl sulfate, alkyl aryl polyether sulfonates, mixtures of sucrose stearate and sucrose distearate, p-isononylphenoxypoly-(glycidol), decanoyl-N-methylglucamide; n-decyl β -D-glucopyranoside; n-decyl β -D-maltopyranoside; n-dodecyl β -D-glucopyranoside; n-dodecyl β -D-maltoside; heptanoyl-N-methylglucamide; n-heptyl- β -D-glucopyranoside; n-heptyl β -D-thioglucoside; n-hexyl β -D-glucopyranoside; nonanoyl-N-methylglucamide; n-nonyl β -D-glucopyranoside; octanoyl-N-methylglucamide; n-octyl- β -D-glucopyranoside; octyl β -D-thioglucopyranoside; lysozyme, PEG-phospholipid, PEG-cholesterol, PEG-cholesterol derivative, PEG-vitamin A, and random copolymers of vinyl acetate and vinyl pyrrolidone.

12. (Original) The composition of claim 10, wherein the at least one cationic surface stabilizer is selected from the group consisting of a polymer, a biopolymer, a polysaccharide, a cellulosic, an alginate, a nonpolymeric compound, and a phospholipid.

13. (Previously Presented) The composition of claim 10, wherein the surface stabilizer is selected from the group consisting of cationic lipids, polymethylmethacrylate trimethylammonium bromide, sulfonium compounds, polyvinylpyrrolidone-2-dimethylaminoethyl methacrylate dimethyl sulfate, hexadecyltrimethyl ammonium bromide, phosphonium compounds, quarternary ammonium compounds, benzyl-di(2-chloroethyl)ethylammonium bromide, coconut trimethyl ammonium chloride, coconut trimethyl ammonium bromide, coconut methyl dihydroxyethyl ammonium chloride, coconut methyl dihydroxyethyl ammonium bromide, decyl triethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride bromide,

C₁₂₋₁₅dimethyl hydroxyethyl ammonium chloride, C₁₂₋₁₅dimethyl hydroxyethyl ammonium chloride bromide, coconut dimethyl hydroxyethyl ammonium chloride, coconut dimethyl hydroxyethyl ammonium bromide, myristyl trimethyl ammonium methyl sulphate, lauryl dimethyl benzyl ammonium chloride, lauryl dimethyl benzyl ammonium bromide, lauryl dimethyl (ethenoxy)₄ ammonium chloride, lauryl dimethyl (ethenoxy)₄ ammonium bromide, N-alkyl (C₁₂₋₁₈)dimethylbenzyl ammonium chloride, N-alkyl (C₁₄₋₁₈)dimethyl-benzyl ammonium chloride, N-tetradecyldimethylbenzyl ammonium chloride monohydrate, dimethyl didecyl ammonium chloride, N-alkyl and (C₁₂₋₁₄) dimethyl 1-naphthylmethyl ammonium chloride, trimethylammonium halide, alkyl-trimethylammonium salts, dialkyl-dimethylammonium salts, lauryl trimethyl ammonium chloride, ethoxylated alkyamidoalkyldialkylammonium salt, an ethoxylated trialkyl ammonium salt, dialkylbenzene dialkylammonium chloride, N-didecyldimethyl ammonium chloride, N-tetradecyldimethylbenzyl ammonium, chloride monohydrate, N-alkyl(C₁₂₋₁₄) dimethyl 1-naphthylmethyl ammonium chloride, dodecyldimethylbenzyl ammonium chloride, dialkyl benzenealkyl ammonium chloride, lauryl trimethyl ammonium chloride, alkylbenzyl methyl ammonium chloride, alkyl benzyl dimethyl ammonium bromide, C₁₂ trimethyl ammonium bromides, C₁₅ trimethyl ammonium bromides, C₁₇ trimethyl ammonium bromides, dodecylbenzyl triethyl ammonium chloride, poly-diallyldimethylammonium chloride (DADMAC), dimethyl ammonium chlorides, alkyldimethylammonium halogenides, tricetyl methyl ammonium chloride, decyltrimethylammonium bromide, dodecyltriethylammonium bromide, tetradecyltrimethylammonium bromide, methyl trioctylammonium chloride, polyquaternium 10, tetrabutylammonium bromide, benzyl trimethylammonium bromide, choline esters, benzalkonium chloride, stearalkonium chloride compounds, cetyl pyridinium bromide, cetyl pyridinium chloride, halide salts of quaternized polyoxyethylalkylamines, quaternized ammonium salt polymers, alkyl pyridinium salts; amines, amine salts, amine oxides, imide azolinium salts, protonated quaternary acrylamides, methylated quaternary polymers, and cationic guar.

14. (Original) The composition of claim 1, comprising as a surface stabilizer a random copolymer of vinyl acetate and vinyl pyrrolidone, hydroxypropylmethyl cellulose, or tyloxapol.

15. (Original) The composition of any of claims 10, 12, or 13, wherein the composition is bioadhesive.

16. (Original) The composition of claim 1, wherein the T_{\max} of the nimesulide, when assayed in the plasma of a mammalian subject following administration, is less than the T_{\max} for a conventional, non-nanoparticulate form of nimesulide, administered at the same dosage.

17. (Previously Presented) The composition of claim 16, wherein the T_{\max} is selected from the group consisting of not greater than 90%, not greater than 80%, not greater than 70%, not greater than 60%, not greater than 50%, not greater than 30%, not greater than 25%, not greater than 20%, not greater than 15%, and not greater than 10% of the T_{\max} , exhibited by a non-nanoparticulate formulation of nimesulide, administered at the same dosage.

18. (Original) The composition of claim 1, wherein the C_{\max} of the nimesulide, when assayed in the plasma of a mammalian subject following administration, is greater than the C_{\max} for a conventional, non-nanoparticulate form of nimesulide, administered at the same dosage.

19. (Previously Presented) The composition of claim 18, wherein the C_{\max} is selected from the group consisting of at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, and at least 100% greater than the C_{\max} exhibited by a non-nanoparticulate formulation of nimesulide, administered at the same dosage.

20. (Original) The composition of claim 1, wherein the AUC of the nimesulide, when assayed in the plasma of a mammalian subject following administration, is greater than the AUC for a conventional, non-nanoparticulate form of nimesulide, administered at the same dosage.

21. (Previously Presented) The composition of claim 20, wherein the AUC is selected from the group consisting of at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, and at least 100% greater than the AUC exhibited by a non-nanoparticulate formulation of nimesulide, administered at the same dosage.

22. (Previously Presented) The composition of claim 1 which does not produce a difference in the absorption levels of the nimesulide composition when administered to a patient under fed as compared to fasting conditions.

23. (Previously Presented) The composition of claim 22, wherein the difference in absorption of the nimesulide composition of the invention, when administered in the fed versus the fasted state, is selected from the group consisting of less than 100%, less than 90%, less than 80%, less than 70%, less than 60%, less than 50%, less than 40%, less than 30%, less than 25%, less than 20%, less than 15%, less than 10%, less than 5%, and less than 3%.

24. (Original) The composition of claim 1, wherein administration of the composition to a subject in a fasted state is bioequivalent to administration of the composition to a subject in a fed state, when administered to a human.

25. (Original) The composition of claim 24, wherein "bioequivalency" is established by a 90% Confidence Interval of between 0.80 and 1.25 for both C_{max} and AUC, when administered to a human.

26. (Original) The composition of claim 24, wherein "bioequivalency" is established by a 90% Confidence Interval of between 0.80 and 1.25 for AUC and a 90% Confidence Interval of between 0.70 to 1.43 for C_{max} , when administered to a human.

27. (Previously Presented) The composition of claim 1, further comprising at least one additional nimesulide composition having an effective average particle size which is different than the effective average particle size of the nimesulide composition of claim 1.

28. (Previously Presented) The composition of claim 1, wherein upon administration the composition redisperses such that the nimesulide particles have an effective average particle size of less than 2000 nm.

29. (Previously Presented) The composition of claim 28, wherein upon administration the composition redisperses such that the nimesulide particles have an effective average particle size selected from the group consisting of less than 1900 nm, less than 1800 nm, less than 1700 nm, less than 1600 nm, less than 1500 nm, less than 1400 nm, less than 1300 nm, less than 1200 nm, less than 1100 nm, less than 1000 nm, less than 900 nm, less than 800 nm, less than 700 nm, less than 600 nm, less than 500 nm, less than 400 nm, less than 300 nm, less than 250 nm, less than 200 nm, less than 150 nm, less than 100 nm, less than 75 nm, and less than 50 nm.

30. (Previously Presented) The composition of claim 1, wherein the composition redisperses in a biorelevant media such that the nimesulide particles have an effective average particle size of less than 2 microns.

31. (Previously Presented) The composition of claim 30, wherein the composition redisperses in a biorelevant media such that the nimesulide particles have an effective average particle size selected from the group consisting of less than 1900 nm, less than 1800 nm, less than 1700 nm, less than 1600 nm, less than 1500 nm, less than 1400 nm, less than 1300 nm, less than 1200 nm, less than 1100 nm, less than 1000 nm, less than 900 nm, less than 800 nm, less than 700 nm, less than 600 nm, less than 500 nm, less than 400 nm, less than 300 nm, less than 250 nm, less than 200 nm, less than 150 nm, less than 100 nm, less than 75 nm, and less than 50 nm.

32. (Withdrawn) The composition of claim 1 formulated into a liquid dosage form, wherein the dosage form has a viscosity of less than 2000 mPa·s, measured at 20°C, at a shear rate of 0.1 (1/s).

33. (Withdrawn) The composition of claim 32, having a viscosity at a shear rate of 0.1 (1/s) selected from the group consisting of from about 2000 mPa·s to about 1 mPa·s, from about 1900 mPa·s to about 1 mPa·s, from about 1800 mPa·s to about 1 mPa·s, from about 1700 mPa·s to about 1 mPa·s, from about 1600 mPa·s to about 1 mPa·s, from about 1500 mPa·s to about 1 mPa·s, from about 1400 mPa·s to about 1 mPa·s, from about 1300 mPa·s to about 1 mPa·s, from about 1200 mPa·s to about 1 mPa·s, from about 1100 mPa·s to about 1 mPa·s, from about 1000 mPa·s to about 1 mPa·s, from about 900 mPa·s to about 1 mPa·s, from about 800 mPa·s to about 1 mPa·s, from about 700 mPa·s to about 1 mPa·s, from about 600 mPa·s to about 1 mPa·s, from about 500 mPa·s to about 1 mPa·s, from about 400 mPa·s to about 1 mPa·s, from about 300 mPa·s to about 1 mPa·s, from about 200 mPa·s to about 1 mPa·s, from about 175 mPa·s to about 1 mPa·s, from about 150 mPa·s to about 1 mPa·s, from about 125 mPa·s to about 1 mPa·s, from about 100 mPa·s to about 1 mPa·s, from about 75 mPa·s to about 1 mPa·s, from about 50 mPa·s to about 1 mPa·s, from about 25 mPa·s to about 1 mPa·s, from about 15 mPa·s to about 1 mPa·s, from about 10 mPa·s to about 1 mPa·s, and from about 5 mPa·s to about 1 mPa·s.

34. (Withdrawn) The composition of claim 32, wherein the viscosity of the dosage form is selected from the group consisting of less than 1/200, less than 1/100, less than 1/50, less than 1/25, and less than 1/10 of the viscosity of a liquid dosage form of conventional non-nanoparticulate nimesulide at about the same concentration per ml of nimesulide.

35. (Withdrawn) The composition of claims 32, wherein the viscosity of the dosage form is selected from the group consisting of less than 5%, less than 10%, less than 15%, less than 20%, less than 25%, less than 30%, less than 35%, less than 40%, less than 45%, less than 50%, less than 55%, less than 60%, less than 65%, less than 70%, less than 75%, less than 80%,

less than 85%, and less than 90% of the viscosity of a liquid dosage form of conventional, non-nanoparticulate nimesulide at about the same concentration per ml of nimesulide.

36. (Original) The composition of claim 1, additionally comprising one or more non-nimesulide active agents.

37. (Previously Presented) The composition of claim 36, wherein said non-nimesulide active agent is selected from the group consisting of an analgesic, an anti-inflammatory, an antipyretic, and a vasomodulator.

38. (Original) The composition of claim 36, wherein said non-nimesulide active agent is selected from the group consisting of nutraceuticals, proteins, peptides, nucleotides, amino acids, anti-obesity drugs, central nervous system stimulants, carotenoids, corticosteroids, elastase inhibitors, anti-fungals, oncology therapies, anti-emetics, analgesics, cardiovascular agents, anti-inflammatory agents, NSAIDs, non-nimesulide COX-2 inhibitors, anthelmintics, anti-arrhythmic agents, antibiotics, anticoagulants, antidepressants, antidiabetic agents, antiepileptics, antihistamines, antihypertensive agents, antimuscarinic agents, antimycobacterial agents, antineoplastic agents, immunosuppressants, antithyroid agents, antiviral agents, anxiolytics, sedatives, astringents, alpha-adrenergic receptor blocking agents, beta-adrenoceptor blocking agents, blood products and substitutes, cardiac inotropic agents, contrast media, corticosteroids, cough suppressants, diagnostic agents, diagnostic imaging agents, diuretics, dopaminergics, haemostatics, immunological agents, lipid regulating agents, muscle relaxants, parasympathomimetics, parathyroid calcitonin and biphosphonates, prostaglandins, radio-pharmaceuticals, sex hormones, anti-allergic agents, stimulants and anoretics, sympathomimetics, thyroid agents, vasodilators, vasomodulators, and xanthines.

39. (Withdrawn) The composition of claim 38, wherein said nutraceutical is selected from the group consisting of lutein, folic acid, fatty acids, fruit extracts, vegetable extracts, vitamin supplements, mineral supplements, phosphatidylserine, lipoic acid, melatonin,

glucosamine/chondroitin, Aloe Vera, Guggul, glutamine, amino acids, green tea, lycopene, whole foods, food additives, herbs, phytonutrients, antioxidants, flavonoid constituents of fruits, evening primrose oil, flax seeds, fish oils, marine animal oils, and probiotics.

40. (Original) The composition of claim 36, wherein said non-nimesulide active agent is selected from the group consisting of aceclofenac, acemetacin, e-acetamidocaproic acid, acetaminophen, acetaminosalol, acetanilide, acetylsalicylic acid, S-adenosylmethionine, alclofenac, alfentanil, allylprodine, alminoprofen, aloxiprin, alphaprodine, aluminum bis(acetylsalicylate), amfenac, aminochlorthenoxazin, 3-amino-4-hydroxybutyric acid, 2-amino-4-picoline, aminopropyl, aminopyrine, amixetrine, ammonium salicylate, ampiroxicam, amtolmetin guacil, anileridine, antipyrine, antipyrine salicylate, antrafenine, apazone, bendazac, benorylate, benoxaprofen, benzpiperylon, benzydamine, benzylmorphine, bermoprofen, bezitramide, α -bisabolol, bromfenac, p-bromoacetanilide, 5-bromosalicylic acid acetate, bromosaligenin, buccetin, bucloxic acid, bucolome, bufexamac, bumadizon, buprenorphine, butacetin, butibufen, butophanol, calcium acetylsalicylate, carbamazepine, carbiphen, carprofen, carsalam, chlorobutanol, chlorthenoxazin, choline salicylate, cinchophen, cinmetacin, cirmadol, clidanac, clometacin, clonitazene, clonixin, clopirac, clove, codeine, codeine methyl bromide, codeine phosphate, codeine sulfate, cropropamide, crotethamide, desomorphine, dexoadrol, dextromoramide, dezocine, diampromide, diclofenac sodium, difenamizole, difenpiramide, diflunisal, dihydrocodeine, dihydrocodeinone enol acetate, dihydromorphine, dihydroxyaluminum acetylsalicylate, dimenoxadol, dimepheptanol, dimethylthiambutene, dioxaphetyl butyrate, dipipanone, diprocetyl, dipyrone, ditazol, droxicam, emorfazone, enfenamic acid, eprizole, eptazocine, etersalate, ethenzamide, ethoheptazine, ethoxazene, ethylmethylthiambutene, ethylmorphine, etodolac, etofenamate, etonitazene, eugenol, felbinac, fenbufen, fenclozic acid, fendosal, fenoprofen, fentanyl, fentiazac, fepradinol, feprazone, floctafenine, flufenamic acid, flunoxaprofen, fluoresone, flupirtine, fluproquazone, flurbiprofen, fosfosal, gentisic acid, glafenine, glucametacin, glycol salicylate, guaiazulene, hydrocodone, hydromorphone, hydroxypethidine, ibufenac, ibuprofen, ibuproxam, imidazole salicylate,

indomethacin, indoprofen, isofezolac, isoladol, isomethadone, isonixin, isoxepac, isoxicam, ketobemidone, ketoprofen, ketorolac, p-lactophenetide, lefetamine, levorphanol, lofentanil, lonazolac, lomoxicam, loxoprofen, lysine acetylsalicylate, magnesium acetylsalicylate, meclofenamic acid, mefenamic acid, meperidine, meptazinol, mesalamine, metazocine, methadone hydrochloride, methotrimeprazine, metiazinic acid, metofoline, metopon, mofebutazone, mofezolac, morazone, morphine, morphine hydrochloride, morphine sulfate, morpholine salicylate, myrophine, nabumetone, nalbuphine, 1-naphthyl salicylate, naproxen, narceine, nefopam, nicomorphine, nifenazone, niflumic acid, nimesulide, 5'-nitro-2'-propoxyacetanilide, norlevorphanol, normethadone, normorphine, norpipanone, olsalazine, opium, oxaceprol, oxametacine, oxaprozin, oxycodone, oxymorphone, oxyphenbutazone, papaveretum, paranyline, parsalmide, pentazocine, perisoxal, phenacetin, phenadoxone, phenazocine, phenazopyridine hydrochloride, phenocoll, phenoperidine, phenopyrazone, phenyl acetylsalicylate, phenylbutazone, phenyl salicylate, phenyramidol, piketoprofen, piminodine, pipebuzone, piperylone, piprofen, pirazolac, piritramide, piroxicam, pranoprofen, proglumetacin, proheptazine, promedol, propacetamol, propiram, propoxyphene, propyphenazone, proquazone, protizinic acid, ramifenazone, remifentanil, rimazolium metilsulfate, salacetamide, salicin, salicylamide, salicylamide o-acetic acid, salicylsulfuric acid, salsalte, salverine, simetride, sodium salicylate, sufentanil, sulfasalazine, sulindac, superoxide dismutase, suprofen, suxibuzone, talniflumate, tenidap, tenoxicam, terofenamate, tetrandrine, thiazolinobutazone, tiaprofenic acid, tiaramide, tilidine, tinoridine, tolfenamic acid, tolmetin, tramadol, tropesin, viminol, xenbucin, ximoprofen, zaltoprofen, and zomepirac.

41. (Withdrawn) The composition of claim 38, in which the vasomodulator is selected from the group consisting of caffeine, theobromine, and theophylline.

42. (Withdrawn) The composition of claim 38, in which the NSAID is selected from the group consisting of nabumetone, tiaramide, proquazone, bufexamac, flumizole, epirazole, tinoridine, timegadine, dapsone, aspirin, diflunisal, benorylate, fosfosal, diclofenac, alclofenac,

fenclofenac, etodolac, indomethacin, sulindac, tolmetin, fentiazac, tilomisole, carprofen, fenbufen, flurbiprofen, ketoprofen, oxaprozin, suprofen, tiaprofenic acid, ibuprofen, naproxen, fenoprofen, indoprofen, pirprofen, flufenamic, mefenamic, meclofenamic, niflumic, oxyphenbutazone, phenylbutazone, apazone, feprazone, piroxicam, sudoxicam, isoxicam, and tenoxicam.

43. (Withdrawn) The composition of claim 38, in which the COX-2 inhibitor is selected from the group consisting of celecoxib, rofecoxib, meloxicam, valdecoxib, parecoxib, etoricoxib, SC-236, NS-398, SC-58125, SC-57666, SC-558, SC-560, etodolac, DFU, monteleukast, L-745337, L-761066, L-761000, L-748780, DUP-697, PGV 20229, iguratimod, BF 389, CL 1004, PD 136005, PD 142893, PD 138387, PD 145065, flurbiprofen, nabumetone, flosulide, piroxicam, diclofenac, lumiracoxib, D 1367, R 807, JTE-522, FK-3311, FK 867, FR 140423, FR 115068, GR 253035, RWJ 63556, RWJ 20485, ZK 38997, S 2474, zomepirac analogs, RS 104894, SC 41930, pranlukast, SB 209670, and APHS

44. (Original) The composition of claim 1, which has been sterile filtered.

45. (Withdrawn) A method of making a nimesulide composition comprising contacting particles of nimesulide or a salt thereof with at least one surface stabilizer for a time and under conditions sufficient to provide a nimesulide composition having an effective average particle size of less than 2000 nm, wherein the at least one surface stabilizer is adsorbed on the surface of the nimesulide particles.

46. (Withdrawn) The method of claim 45, wherein said contacting comprises grinding.

47. (Withdrawn) The method of claim 46, wherein said grinding comprises wet grinding.

48. (Withdrawn) The method of claim 45, wherein said contacting comprises homogenizing.

49. (Withdrawn) The method of claim 45, wherein said contacting comprises:

- (a) dissolving the particles of nimesulide or a salt thereof in a solvent;
- (b) adding the resulting nimesulide solution to a solution comprising at least one surface stabilizer; and
- (c) precipitating the solubilized nimesulide having at least one surface stabilizer adsorbed on the surface thereof by the addition thereto of a non-solvent.

50. (Withdrawn) The method of claim 45, wherein the nimesulide or a salt thereof is selected from the group consisting of a crystalline phase, an amorphous phase, and a semi-crystalline phase.

51. (Withdrawn) The method of claim 45, wherein the effective average particle size of the nimesulide particles is selected from the group consisting of less than 1900 nm, less than 1800 nm, less than 1700 nm, less than 1600 nm, less than 1500 nm, less than 1000 nm, less than 1400 nm, less than 1300 nm, less than 1200 nm, less than 1100 nm, less than 900 nm, less than 800 nm, less than 700 nm, less than 600 nm, less than 500 nm, less than 400 nm, less than 300 nm, less than 250 nm, less than 200 nm, less than 100 nm, less than 75 nm, and less than 50 nm.

52. (Withdrawn) The method of claim 45, wherein the composition is formulated for administration selected from the group consisting of oral, pulmonary, rectal, ophthalmic, colonic, parenteral, intracisternal, intravaginal, intraperitoneal, local, buccal, nasal, and topical administration.

53. (Withdrawn) The method of claim 45, wherein the composition further comprises one or more pharmaceutically acceptable excipients, carriers, or a combination thereof.

54. (Withdrawn) The method of claim 45, wherein the nimesulide or a salt thereof is present in an amount selected from the group consisting of from about 99.5% to about 0.001%, from about 95% to about 0.1%, and from about 90% to about 0.5%, by weight, based on the total combined dry weight of the nimesulide or a salt thereof and at least one surface stabilizer, not including other excipients.

55. (Withdrawn) The method of claim 45, wherein the at least one surface stabilizer is present in an amount selected from the group consisting of from about 0.5% to about 99.999%, from about 5.0% to about 99.9%, and from about 10% to about 99.5% by weight, based on the total combined dry weight of the nimesulide or a salt thereof and at least one surface stabilizer, not including other excipients.

56. (Withdrawn) The method of claim 45, comprising at two surface stabilizers.

57. (Withdrawn) The method of claim 45, wherein the surface stabilizer is selected from the group consisting of an anionic surface stabilizer, a cationic surface stabilizer, a zwitterionic surface stabilizer, a non-ionic surface stabilizer, and an ionic surface stabilizer.

58. (Withdrawn) The method of claim 57, wherein the at least one surface stabilizer is selected from the group consisting of cetyl pyridinium chloride, gelatin, casein, phosphatides, dextran, glycerol, gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glycerol monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers, polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters, polyethylene glycols, dodecyl trimethyl ammonium bromide, polyoxyethylene stearates, colloidal silicon dioxide, phosphates, sodium dodecylsulfate, carboxymethylcellulose calcium, hydroxypropyl celluloses, hypromellose, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hypromellose phthalate, noncrystalline cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol, polyvinylpyrrolidone, 4-(1,1,3,3-tetramethylbutyl)-phenol polymer with ethylene oxide and

formaldehyde, poloxamers; poloxamines, a charged phospholipid, dioctylsulfosuccinate, dialkylesters of sodium sulfosuccinic acid, sodium lauryl sulfate, alkyl aryl polyether sulfonates, mixtures of sucrose stearate and sucrose distearate, p-isononylphenoxypoly-(glycidol), decanoyl-N-methylglucamide; n-decyl β -D-glucopyranoside; n-decyl β -D-maltopyranoside; n-dodecyl β -D-glucopyranoside; n-dodecyl β -D-maltoside; heptanoyl-N-methylglucamide; n-heptyl- β -D-glucopyranoside; n-heptyl β -D-thioglucoside; n-hexyl β -D-glucopyranoside; nonanoyl-N-methylglucamide; n-nonyl β -D-glucopyranoside; octanoyl-N-methylglucamide; n-octyl- β -D-glucopyranoside; octyl β -D-thioglucopyranoside; lysozyme, PEG-phospholipid, PEG-cholesterol, PEG-cholesterol derivative, PEG-vitamin A, PEG-vitamin E, and random copolymers of vinyl acetate and vinyl pyrrolidone.

59. (Withdrawn) The method of claim 57, wherein the at least one cationic surface stabilizer is selected from the group consisting of a polymer, a biopolymer, a polysaccharide, a cellulosic, an alginate, a nonpolymeric compound, and a phospholipid.

60. (Withdrawn) The method of claim 57, wherein the surface stabilizer is selected from the group consisting of cationic lipids, polymethylmethacrylate trimethylammonium bromide, sulfonium compounds, polyvinylpyrrolidone-2-dimethylaminoethyl methacrylate dimethyl sulfate, hexadecyltrimethyl ammonium bromide, phosphonium compounds, quaternary ammonium compounds, benzyl-di(2-chloroethyl)ethylammonium bromide, coconut trimethyl ammonium chloride, coconut trimethyl ammonium bromide, coconut methyl dihydroxyethyl ammonium chloride, coconut methyl dihydroxyethyl ammonium bromide, decyl triethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride bromide, C₁₂₋₁₅dimethyl hydroxyethyl ammonium chloride, C₁₂₋₁₅dimethyl hydroxyethyl ammonium chloride bromide, coconut dimethyl hydroxyethyl ammonium chloride, coconut dimethyl hydroxyethyl ammonium bromide, myristyl trimethyl ammonium methyl sulphate, lauryl dimethyl benzyl ammonium chloride, lauryl dimethyl benzyl ammonium bromide, lauryl dimethyl (ethenoxy)₄ ammonium chloride, lauryl dimethyl

(ethenoxy)₄ ammonium bromide, N-alkyl (C₁₂₋₁₈)dimethylbenzyl ammonium chloride, N-alkyl (C₁₄₋₁₈)dimethyl-benzyl ammonium chloride, N-tetradecyldimethylbenzyl ammonium chloride monohydrate, dimethyl didecyl ammonium chloride, N-alkyl and (C₁₂₋₁₄) dimethyl 1-naphthylmethyl ammonium chloride, trimethylammonium halide, alkyl-trimethylammonium salts, dialkyl-dimethylammonium salts, lauryl trimethyl ammonium chloride, ethoxylated alkyamidoalkyldialkylammonium salt, an ethoxylated trialkyl ammonium salt, dialkylbenzene dialkylammonium chloride, N-didecyldimethyl ammonium chloride, N-tetradecyldimethylbenzyl ammonium, chloride monohydrate, N-alkyl(C₁₂₋₁₄) dimethyl 1-naphthylmethyl ammonium chloride, dodecyldimethylbenzyl ammonium chloride, dialkyl benzenealkyl ammonium chloride, lauryl trimethyl ammonium chloride, alkylbenzyl methyl ammonium chloride, alkyl benzyl dimethyl ammonium bromide, C₁₂ trimethyl ammonium bromides, C₁₅ trimethyl ammonium bromides, C₁₇ trimethyl ammonium bromides, dodecylbenzyl triethyl ammonium chloride, polydiallyldimethylammonium chloride (DADMAC), dimethyl ammonium chlorides, alkyldimethylammonium halogenides, tricetyl methyl ammonium chloride, decyltrimethylammonium bromide, dodecyltriethylammonium bromide, tetradecyltrimethylammonium bromide, methyl trioctylammonium chloride, polyquaternium 10, tetrabutylammonium bromide, benzyl trimethylammonium bromide, choline esters, benzalkonium chloride, stearalkonium chloride compounds, cetyl pyridinium bromide, cetyl pyridinium chloride, halide salts of quaternized polyoxyethylalkylamines, quaternized ammonium salt polymers, alkyl pyridinium salts; amines, amine salts, amine oxides, imide azolinium salts, protonated quaternary acrylamides, methylated quaternary polymers, and cationic guar.

61. (Withdrawn) The method of claim 45, utilizing as a surface stabilizer a random copolymer of vinyl acetate and vinyl pyrrolidone, hydroxypropylmethyl cellulose, or tyloxapol.

62. (Withdrawn) The method of any of claims 57, 59, or 60, wherein the composition is bioadhesive.

63. (Withdrawn) A method of treating a subject in need comprising administering to the subject an effective amount of a composition comprising:

- (a) particles of nimesulide or a salt thereof, wherein the nimesulide particles have an effective average particle size of less than 2000 nm; and
- (b) at least one surface stabilizer adsorbed on the surface of the nimesulide particles.

64. (Withdrawn) The method of claim 63, wherein the nimesulide or a salt thereof is selected from the group consisting of a crystalline phase, an amorphous phase, and a semi-crystalline phase.

65. (Withdrawn) The method of claim 63, wherein the effective average particle size of the nimesulide particles is selected from the group consisting of less than 1900 nm, less than 1800 nm, less than 1700 nm, less than 1600 nm, less than 1500 nm, less than 1400 nm, less than 1300 nm, less than 1200 nm, less than 1100 nm, less than 1000 nm, less than 900 nm, less than 800 nm, less than 700 nm, less than 600 nm, less than 500 nm, less than 400 nm, less than 300 nm, less than 250 nm, less than 200 nm, less than 100 nm, less than 75 nm, and less than 50 nm.

66. (Withdrawn) The method of claim 63, wherein the composition is formulated for administration selected from the group consisting of oral, pulmonary, rectal, ophthalmic, colonic, parenteral, intracisternal, intravaginal, intraperitoneal, local, buccal, nasal, and topical administration.

67. (Withdrawn) The method of claim 63, wherein the composition is a dosage form selected from the group consisting of liquid dispersions, oral suspensions, gels, aerosols, ointments, creams, controlled release formulations, fast melt formulations, lyophilized formulations, tablets, capsules, delayed release formulations, extended release formulations, pulsatile release formulations, and mixed immediate release and controlled release formulations.

68. (Withdrawn) The method of claim 63, wherein the composition further comprises one or more pharmaceutically acceptable excipients, carriers, or a combination thereof.

69. (Withdrawn) The method of claim 63, wherein the nimesulide or a salt thereof is present in an amount selected from the group consisting of from about 99.5% to about 0.001%, from about 95% to about 0.1%, and from about 90% to about 0.5%, by weight, based on the total combined dry weight of the nimesulide or a salt thereof and at least one surface stabilizer, not including other excipients.

70. (Withdrawn) The method of claim 63, wherein the at least one surface stabilizer is present in an amount selected from the group consisting of from about 0.5% to about 99.999% by weight, from about 5.0% to about 99.9% by weight, and from about 10% to about 99.5% by weight, based on the total combined dry weight of the nimesulide or a salt thereof and at least one surface stabilizer, not including other excipients.

71. (Withdrawn) The method of claim 63, comprising at two surface stabilizers.

72. (Withdrawn) The method of claim 63, wherein the surface stabilizer is selected from the group consisting of an anionic surface stabilizer, a cationic surface stabilizer, a zwitterionic surface stabilizer, a non-ionic surface stabilizer, and an ionic surface stabilizer.

73. (Withdrawn) The method of claim 72, wherein the at least one surface stabilizer is selected from the group consisting of cetyl pyridinium chloride, gelatin, casein, phosphatides, dextran, glycerol, gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glycerol monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers, polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters, polyethylene glycols, dodecyl trimethyl ammonium bromide, polyoxyethylene stearates, colloidal silicon dioxide, phosphates, sodium dodecylsulfate, carboxymethylcellulose calcium, hydroxypropyl celluloses, hypromellose, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hypromellose phthalate, noncrystalline cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol, polyvinylpyrrolidone, 4-(1,1,3,3-tetramethylbutyl)-phenol polymer with ethylene oxide and

formaldehyde, poloxamers; poloxamines, a charged phospholipid, dioctylsulfosuccinate, dialkylesters of sodium sulfosuccinic acid, sodium lauryl sulfate, alkyl aryl polyether sulfonates, mixtures of sucrose stearate and sucrose distearate, p-isononylphenoxypoly-(glycidol), decanoyl-N-methylglucamide; n-decyl β -D-glucopyranoside; n-decyl β -D-maltopyranoside; n-dodecyl β -D-glucopyranoside; n-dodecyl β -D-maltoside; heptanoyl-N-methylglucamide; n-heptyl- β -D-glucopyranoside; n-heptyl β -D-thioglucoside; n-hexyl β -D-glucopyranoside; nonanoyl-N-methylglucamide; n-nonyl β -D-glucopyranoside; octanoyl-N-methylglucamide; n-octyl- β -D-glucopyranoside; octyl β -D-thioglucopyranoside; lysozyme, PEG-phospholipid, PEG-cholesterol, PEG-cholesterol derivative, PEG-vitamin A, PEG-vitamin E, and random copolymers of vinyl acetate and vinyl pyrrolidone.

74. (Withdrawn) The method of claim 72, wherein the at least one cationic surface stabilizer is selected from the group consisting of a polymer, a biopolymer, a polysaccharide, a cellulosic, an alginate, a nonpolymeric compound, and a phospholipid.

75. (Withdrawn) The method of claim 72, wherein the surface stabilizer is selected from the group consisting of benzalkonium chloride, polymethylmethacrylate trimethylammonium bromide, polyvinylpyrrolidone-2-dimethylaminoethyl methacrylate dimethyl sulfate, hexadecyltrimethyl ammonium bromide, cationic lipids, sulfonium compounds, phosphonium compounds, quaternary ammonium compounds, benzyl-di(2-chloroethyl)ethylammonium bromide, coconut trimethyl ammonium chloride, coconut trimethyl ammonium bromide, coconut methyl dihydroxyethyl ammonium chloride, coconut methyl dihydroxyethyl ammonium bromide, decyl triethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride bromide, C₁₂₋₁₅dimethyl hydroxyethyl ammonium chloride, C₁₂₋₁₅dimethyl hydroxyethyl ammonium chloride bromide, coconut dimethyl hydroxyethyl ammonium chloride, coconut dimethyl hydroxyethyl ammonium bromide, myristyl trimethyl ammonium methyl sulphate, lauryl dimethyl benzyl ammonium chloride, lauryl dimethyl benzyl ammonium bromide, lauryl

dimethyl (ethenoxy)₄ ammonium chloride, lauryl dimethyl (ethenoxy)₄ ammonium bromide, N-alkyl (C₁₂₋₁₈)dimethylbenzyl ammonium chloride, N-alkyl (C₁₄₋₁₈)dimethyl-benzyl ammonium chloride, N-tetradecyldimethylbenzyl ammonium chloride monohydrate, dimethyl didecyl ammonium chloride, N-alkyl and (C₁₂₋₁₄) dimethyl 1-naphthylmethyl ammonium chloride, trimethylammonium halide, alkyl-trimethylammonium salts, dialkyl-dimethylammonium salts, lauryl trimethyl ammonium chloride, ethoxylated alkyamidoalkyldialkylammonium salt, an ethoxylated trialkyl ammonium salt, dialkylbenzene dialkylammonium chloride, N-didecyldimethyl ammonium chloride, N-tetradecyldimethylbenzyl ammonium, chloride monohydrate, N-alkyl(C₁₂₋₁₄) dimethyl 1-naphthylmethyl ammonium chloride, dodecyldimethylbenzyl ammonium chloride, dialkyl benzenealkyl ammonium chloride, lauryl trimethyl ammonium chloride, alkylbenzyl methyl ammonium chloride, alkyl benzyl dimethyl ammonium bromide, C₁₂ trimethyl ammonium bromides, C₁₅ trimethyl ammonium bromides, C₁₇ trimethyl ammonium bromides, dodecylbenzyl triethyl ammonium chloride, polydiallyldimethylammonium chloride (DADMAC), dimethyl ammonium chlorides, alkyldimethylammonium halogenides, tricetyl methyl ammonium chloride, decyltrimethylammonium bromide, dodecyltriethylammonium bromide, tetradecyltrimethylammonium bromide, methyl trioctylammonium chloride, polyquaternium 10, tetrabutylammonium bromide, benzyl trimethylammonium bromide, choline esters, benzalkonium chloride, stearalkonium chloride compounds, cetyl pyridinium bromide, cetyl pyridinium chloride, halide salts of quaternized polyoxyethylalkylamines, quaternized ammonium salt polymers, alkyl pyridinium salts; amines, amine salts, amine oxides, imide azolinium salts, protonated quaternary acrylamides, methylated quaternary polymers, and cationic guar.

76. (Withdrawn) The method of claim 63, utilizing as a surface stabilizer a random copolymer of vinyl acetate and vinyl pyrrolidone, hydroxypropylmethyl cellulose, or tyloxapol.

77. (Withdrawn) The method of any of claims 72, 74, or 75, wherein the composition is bioadhesive.

78. (Withdrawn) The method of claim 63, wherein administration of the nimesulide composition does not produce a difference in the absorption levels of the nimesulide composition when administered to a patient under fed as compared to fasting conditions, when administered to a human.

79. (Withdrawn) The method of claim 78, wherein the difference in absorption of the nimesulide composition of the invention, when administered in the fed versus the fasted state, is selected from the group consisting of less than 100%, less than 90%, less than 80%, less than 70%, less than 60%, less than 50%, less than 40%, less than 30%, less than 25%, less than 20%, less than 15%, less than 10%, less than 5%, and less than 3%.

80. (Withdrawn) The method of claim 63, wherein administration of the composition to a subject in a fasted state is bioequivalent to administration of the composition to a subject in a fed state, when administered to a human.

81. (Withdrawn) The method of claim 80, wherein "bioequivalency" is established by a 90% Confidence Interval of between 0.80 and 1.25 for both C_{max} and AUC, when administered to a human.

82. (Withdrawn) The method of claim 80, wherein "bioequivalency" is established by a 90% Confidence Interval of between 0.80 and 1.25 for AUC and a 90% Confidence Interval of between 0.70 to 1.43 for C_{max} , when administered to a human.

83. (Withdrawn) The method of claim 63, wherein the T_{max} of the nimesulide, when assayed in the plasma of a mammalian subject following administration, is less than the T_{max} for a conventional, non-nanoparticulate form of nimesulide, administered at the same dosage.

84. (Withdrawn) The method of claim 83, wherein the T_{\max} is selected from the group consisting of not greater than 90%, not greater than 80%, not greater than 70%, not greater than 60%, not greater than 50%, not greater than 30%, not greater than 25%, not greater than 20%, not greater than 15%, and not greater than 10% of the T_{\max} , exhibited by a non-nanoparticulate formulation of nimesulide, administered at the same dosage.

85. (Withdrawn) The method of claim 63, wherein the C_{\max} of the nimesulide, when assayed in the plasma of a mammalian subject following administration, is greater than the C_{\max} for a conventional, non-nanoparticulate form of nimesulide, administered at the same dosage.

86. (Withdrawn) The method of claim 85, wherein the C_{\max} is selected from the group consisting of at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, and at least 100% greater than the C_{\max} exhibited by a non-nanoparticulate formulation of nimesulide, administered at the same dosage.

87. (Withdrawn) The method of claim 63, wherein the AUC of the nimesulide, when assayed in the plasma of a mammalian subject following administration, is greater than the AUC for a conventional, non-nanoparticulate form of nimesulide, administered at the same dosage.

88. (Withdrawn) The method of claim 87, wherein the AUC is selected from the group consisting of at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, and at least 100% greater than the AUC exhibited by a non-nanoparticulate formulation of nimesulide, administered at the same dosage.

89. (Withdrawn) The method of claim 63, additionally comprising administering one or more non-nimesulide active agents.

90. (Withdrawn) The method of claim 63, additionally comprising administering one or more non-nimesulide active agents effective for treating fever, inflammation or pain.

91. (Withdrawn) The method of claim 89, wherein said non-nimesulide active agent is selected from the group consisting of an analgesic, an anti-inflammatory, an antipyretic, and a vasomodulator.

92. (Withdrawn) The method of claim 89, wherein said non-nimesulide active agent is selected from the group consisting of nutraceuticals, proteins, peptides, nucleotides, amino acids, anti-obesity drugs, central nervous system stimulants, carotenoids, corticosteroids, elastase inhibitors, anti-fungals, oncology therapies, anti-emetics, analgesics, cardiovascular agents, anti-inflammatory agents, NSAIDs, non-nimesulide COX-2 inhibitors, anthelmintics, anti-arrhythmic agents, antibiotics, anticoagulants, antidepressants, antidiabetic agents, antiepileptics, antihistamines, antihypertensive agents, antimuscarinic agents, antimycobacterial agents, antineoplastic agents, immunosuppressants, antithyroid agents, antiviral agents, anxiolytics, sedatives, astringents, alpha-adrenergic receptor blocking agents, beta-adrenoceptor blocking agents, blood products and substitutes, cardiac inotropic agents, contrast media, corticosteroids, cough suppressants, diagnostic agents, diagnostic imaging agents, diuretics, dopaminergics, haemostatics, immunological agents, lipid regulating agents, muscle relaxants, parasympathomimetics, parathyroid calcitonin and biphosphonates, prostaglandins, radio-pharmaceuticals, sex hormones, anti-allergic agents, stimulants and anoretics, sympathomimetics, thyroid agents, vasodilators, vasomodulators, and xanthines.

93. (Withdrawn) The method of claim 63, wherein the subject is a human.

94. (Withdrawn) The method of claim 63, wherein the method is used to treat a condition selected from the group consisting of rheumatic and joint diseases, arthritis, rheumatoid arthritis, osteoarthritis, periartthritis, tendonitis, bursitis, ankylosing spondylitis, joint stiffness, lower back pain, gynecological conditions, menstrual migraine attack, dysmenorrhoea, pelvic inflammatory disease, urological conditions, urethritis, prostatitis, and vesiculitis pyrexia, cardiovascular diseases, atherosclerosis, hypotension, thrombophlebitis, arthrosis; inflammatory conditions, otitis, rhinitis, sinusitis, pharyngitis, bronchitis nephrotoxicity, mastitis, asthma,

cancer, trauma, surgery, migraine headaches, kidney disease, Alzheimer's disease, familial adenomatous polyposis, diarrhea, colonic adenomas bone resorption, and related conditions.

95. (Withdrawn) The method of claim 63, wherein the method is used to treat a condition where anti-inflammatory agents, anti-angiogenesis agents, antitumorigenic agents, immunosuppressive agents, NSAIDs, COX-2 inhibitors, analgesic agents, anti-thrombotic agents, narcotics, or antifebrile agents are typically used.

AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions, and listings, of claims in the application.

Listing of Claims:

1. (Currently amended) A nanoparticulate composition comprising the compound 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methylmorpholine, or a pharmaceutically acceptable salt thereof, the compound having adsorbed on the surface thereof at least one surface stabilizer in an amount sufficient to maintain an effective average particle size of less than ~~1000~~ 400 nm.

2. (Canceled)

3. (Currently amended) The composition of Claim 2-1 wherein the nanoparticles have an effective average particle size of less than 250 nm.

4. (Original) The composition of Claim 1 wherein the surface stabilizer is selected from hydroxypropyl cellulose, hydroxypropyl methyl cellulose, hydroxypropyl cellulose-super low viscosity, hydroxypropyl cellulose-low viscosity, polyvinylpyrrolidone, block copolymers of ethylene oxide and propylene oxide, dioctyl sodium sulfosuccinate and sodium lauryl sulfate.

5. (Original) The composition of Claim 3 wherein the surface stabilizer is hydroxypropyl cellulose-super low viscosity or sodium lauryl sulfate.

6. (Original) A pharmaceutical composition comprising the nanoparticulate composition of Claim 1 and a pharmaceutically acceptable carrier.

7. (Original) A pharmaceutical composition comprising the nanoparticulate composition of Claim 1 which has been spray dried or spray coated on a solid support.

8. (Original) The pharmaceutical composition of Claim 7 wherein the solid support is selected from microcrystalline cellulose spheres, sugar-starch spheres and lactose spheres.

9. (Previously presented) A pharmaceutical composition comprising the compound 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methylmorpholine having a particle size of less than 400 nm, a surface stabilizer, a redispersing agent and a solid support.

10. (Currently amended) The pharmaceutical composition of Claim 9 comprising about 5-60% by weight of 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluoro)-phenyl-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methylmorpholine having a particle size of less than ~~1000~~ 400 nm; about 1-20% by weight of a surface stabilizer; about 0-50% by weight of a redispersing agent; about 0-90% by weight of a solid support; and about 0-5% by weight of a lubricant.

11. (Currently amended) The pharmaceutical composition of Claim 10 comprising about 25-50% by weight of 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methylmorpholine having a particle size of less than ~~1000~~ 400 nm; about 5-15% by weight of a surface stabilizer; about 0-50% by weight of a redispersing agent; about 10-50% by weight of a solid support; and about 0-5% by weight of a lubricant.

12. (Currently amended) A pharmaceutical composition comprising about 5-60% by weight of 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methylmorpholine having a particle size of less than ~~1000~~ 400 nm; about 1-20% by weight of hydroxypropyl cellulose; about 10-50% by weight of sucrose; about 5-80% by weight of microcrystalline cellulose; and about 0-5% by weight of sodium lauryl sulfate.

13. (Currently amended) The pharmaceutical composition of Claim 12 comprising about 10-50% by weight of 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluoro)-phenyl-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methylmorpholine having a particle size of less than ~~1000~~ 400 nm; about 2-15% by weight of hydroxypropyl cellulose; about 10-50% by weight of sucrose; about 5-60% by weight of microcrystalline cellulose; and about 0-2% by weight of sodium lauryl sulfate.

14. (Original) The pharmaceutical composition of Claim 13 comprising about 30-45% by weight of 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl-morpholine; about 5-10% by weight of hydroxypropyl cellulose; about 30-45% by weight of sucrose; about 15-20% by weight of microcrystalline cellulose; and about 0-0.5% by weight of sodium lauryl sulfate.

15. (Withdrawn) A method for antagonizing the effect of substance P at its receptor site or for the blockade of neurokinin-1 receptors in a patient which comprises the administration to the patient of the composition of Claim 1 in an amount that is effective for antagonizing the effect of substance P at its receptor site in the patient.

16. (Withdrawn) A method for treating depression in a patient in need thereof which comprises administering to the patient an effective amount of the composition of Claim 1.

17. (Withdrawn) A method for treating or preventing anxiety in a patient in need thereof which comprises administering to the patient an effective amount of the composition of Claim 1.

18. (Withdrawn) A method for treating or preventing emesis in a patient in need thereof which comprises administering to the patient an effective amount of the composition of Claim 1.

We claim:

1. A nanoparticulate angiogenesis inhibitor composition comprising:
 - (a) particles of an angiogenesis inhibitor or a salt thereof having an effective average particle size of less than about 2000 nm;
and
 - (b) associated with the surface thereof at least one surface stabilizer.
2. The composition of claim 1, wherein the angiogenesis inhibitor is selected from the group consisting of 2-methoxyestradiol, prinomastat, batimastat, BAY 12-9566, carboxyamidotriazole, CC-1088, dextromethorphan acetic, dimethylxanthenone acetic acid, EMD 121974, endostatin, IM-862, marimastat, matrix metalloproteinase, penicillamine, PTK787/ZK 222584, RPI.4610, squalamine, squalamine lactate, SU5416, (\pm)-thalidomide, S- thalidomide, R- thalidomide, TNP-470, combretastatin, paclitaxel, tamoxifen, COL-3, neovastat, BMS-275291, SU6668, interferon-alpha, anti-VEGF antibody, Medi-522 (Vitaxin II), CAI, celecoxib, Interleukin-12, IM862, Amilloride, Angiostatin® Protein, Angiostatin K1-3, Angiostatin K1-5, Captopril, DL-alpha-Difluoromethylornithine, DL-alpha-Difluoromethylornithine HCl, His-Tag® Endostatin™ Protein, Fumagillin, Herbimycin A, 4-Hydroxyphenylretinamide, gamma-interferon, Juglone, Laminin, Laminin Hexapeptide, Laminin Pentapeptide, Lavendustin A, Medroxyprogesterone, Medroxyprogesterone Acetate, Minocycline, Minocycline HCl, Placental Ribonuclease Inhibitor, Suramin, Sodium Salt Suramin, Human Platelet Thrombospondin, Tissue Inhibitor of Metalloproteinase 1, Neutrophil Granulocyte Tissue Inhibitor of Metalloproteinase 1, and Rheumatoid Synovial Fibroblast Tissue Inhibitor of Metalloproteinase 2.
3. The composition of claim 1, wherein the angiogenesis inhibitor is 2-methoxyestradiol.
4. The composition of claim 1, wherein the effective average particle size of the nanoparticulate angiogenesis inhibitor is selected from the group consisting of less than about 1900 nm, less than about 1800 nm, less than about 1700 nm, less than about 1600 nm, less than about 1500 nm, less than about 1400 nm, less than about 1300 nm,

less than about 1200 nm, less than about 1100 nm, less than about 1000 nm, less than about 900 nm, less than about 800 nm, less than about 700 nm, less than about 600 nm, less than about 500 nm, less than about 400 nm, less than about 300 nm, less than about 250 nm, less than about 200 nm, less than about 100 nm, less than about 75 nm, and less than about 50 nm.

5. The composition of claim 1, wherein the composition is formulated for administration selected from the group consisting of oral, pulmonary, rectal, ophthalmic, colonic, parenteral, intracisternal, intravaginal, intraperitoneal, local, buccal, nasal, and topical administration.

6. The composition of claim 1, wherein the composition is formulated into a dosage form selected from the group consisting of liquid dispersions, gels, aerosols, ointments, creams, controlled release formulations, fast melt formulations, lyophilized formulations, tablets, capsules, delayed release formulations, extended release formulations, pulsatile release formulations, and mixed immediate release and controlled release formulations.

7. The composition of claim 1, wherein the composition further comprises one or more pharmaceutically acceptable excipients, carriers, or a combination thereof.

8. The composition of claim 1, wherein the angiogenesis inhibitor is present in an amount selected from the group consisting of from about 99.5% to about 0.001%, from about 95% to about 0.1%, and from about 90% to about 0.5%, by weight, based on the total combined weight of the angiogenesis inhibitor and at least one surface stabilizer, not including other excipients.

9. The composition of claim 1, wherein the at least one surface stabilizer is present in an amount selected from the group consisting of from about 0.5% to about 99.999%, from about 5.0% to about 99.9%, and from about 10% to about 99.5%, by weight, based on the total combined weight of the at least one angiogenesis inhibitor and at least one surface stabilizer, not including other excipients.

10. The composition of claim 1, comprising at least two surface stabilizers.

11. The composition of claim 1, wherein the surface stabilizer is selected from the group consisting of an anionic surface stabilizer, a cationic surface stabilizer, an ionic surface stabilizer, and a zwitterionic surface stabilizer.

12. The composition of claim 11, wherein at least one surface stabilizer is selected from the group consisting of cetyl pyridinium chloride, gelatin, casein, phosphatides, dextran, glycerol, gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glycerol monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers, polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters, polyethylene glycols, dodecyl trimethyl ammonium bromide, polyoxyethylene stearates, colloidal silicon dioxide, phosphates, sodium dodecylsulfate, carboxymethylcellulose calcium, hydroxypropyl celluloses, hydroxypropyl methylcellulose, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hydroxypropylmethyl-cellulose phthalate, noncrystalline cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol, polyvinylpyrrolidone, 4-(1,1,3,3-tetramethylbutyl)-phenol polymer with ethylene oxide and formaldehyde, poloxamers; poloxamines, a charged phospholipid, dioctylsulfosuccinate, dialkylesters of sodium sulfosuccinic acid, sodium lauryl sulfate, alkyl aryl polyether sulfonates, mixtures of sucrose stearate and sucrose distearate, $C_{18}H_{37}CH_2C(O)N(CH_3)-CH_2(CHOH)_4(CH_2OH)_2$, p-isononylphenoxypoly-(glycidol), decanoyl-N-methylglucamide; n-decyl β -D-glucopyranoside; n-decyl β -D-maltopyranoside; n-dodecyl β -D-glucopyranoside; n-dodecyl β -D-maltoside; heptanoyl-N-methylglucamide; n-heptyl- β -D-glucopyranoside; n-heptyl β -D-thioglucoside; n-hexyl β -D-glucopyranoside; nonanoyl-N-methylglucamide; n-nonyl β -D-glucopyranoside; octanoyl-N-methylglucamide; n-octyl- β -D-glucopyranoside; octyl β -D-thioglucopyranoside; lysozyme, PEG-phospholipid, PEG-cholesterol, PEG-cholesterol derivative, PEG-vitamin A, PEG-vitamin E, and random copolymers of vinyl acetate and vinyl pyrrolidone.

13. The composition of claim 11, wherein the surface stabilizer is selected from the group consisting of cationic lipids, polymethylmethacrylate trimethylammonium bromide, sulfonium compounds, polyvinylpyrrolidone-2-dimethylaminoethyl

methacrylate dimethyl sulfate, hexadecyltrimethyl ammonium bromide, phosphonium compounds, quarternary ammonium compounds, benzyl-di(2-chloroethyl)ethylammonium bromide, coconut trimethyl ammonium chloride, coconut trimethyl ammonium bromide, coconut methyl dihydroxyethyl ammonium chloride, coconut methyl dihydroxyethyl ammonium bromide, decyl triethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride bromide, C₁₂₋₁₅dimethyl hydroxyethyl ammonium chloride, C₁₂₋₁₅dimethyl hydroxyethyl ammonium chloride bromide, coconut dimethyl hydroxyethyl ammonium chloride, coconut dimethyl hydroxyethyl ammonium bromide, myristyl trimethyl ammonium methyl sulphate, lauryl dimethyl benzyl ammonium chloride, lauryl dimethyl benzyl ammonium bromide, lauryl dimethyl (ethenoxy)₄ ammonium chloride, lauryl dimethyl (ethenoxy)₄ ammonium bromide, N-alkyl (C₁₂₋₁₈)dimethylbenzyl ammonium chloride, N-alkyl (C₁₄₋₁₈)dimethyl-benzyl ammonium chloride, N-tetradecyldimethylbenzyl ammonium chloride monohydrate, dimethyl didecyl ammonium chloride, N-alkyl and (C₁₂₋₁₄) dimethyl 1-naphthylmethyl ammonium chloride, trimethylammonium halide, alkyl-trimethylammonium salts, dialkyl-dimethylammonium salts, lauryl trimethyl ammonium chloride, ethoxylated alkyamidoalkyldialkylammonium salt, an ethoxylated trialkyl ammonium salt, dialkylbenzene dialkylammonium chloride, N-didecyldimethyl ammonium chloride, N-tetradecyldimethylbenzyl ammonium, chloride monohydrate, N-alkyl(C₁₂₋₁₄) dimethyl 1-naphthylmethyl ammonium chloride, dodecyldimethylbenzyl ammonium chloride, dialkyl benzenealkyl ammonium chloride, lauryl trimethyl ammonium chloride, alkylbenzyl methyl ammonium chloride, alkyl benzyl dimethyl ammonium bromide, C₁₂ trimethyl ammonium bromides, C₁₅ trimethyl ammonium bromides, C₁₇ trimethyl ammonium bromides, dodecylbenzyl triethyl ammonium chloride, poly-diallyldimethylammonium chloride (DADMAC), dimethyl ammonium chlorides, alkyldimethylammonium halogenides, tricetyl methyl ammonium chloride, decyltrimethylammonium bromide, dodecyltriethylammonium bromide, tetradecyltrimethylammonium bromide, methyl trioctylammonium chloride, POLYQUAT 10™, tetrabutylammonium bromide, benzyl trimethylammonium bromide, choline esters, benzalkonium chloride, stearalkonium chloride compounds, cetyl pyridinium bromide,

cetyl pyridinium chloride, halide salts of quaternized polyoxyethylalkylamines, MIRAPOL™, ALKAQUAT™, alkyl pyridinium salts; amines, amine salts, amine oxides, imide azolinium salts, protonated quaternary acrylamides, methylated quaternary polymers, and cationic guar.

14. The composition of claim 13, wherein the composition is bioadhesive.

15. The composition of claim 1, wherein the composition comprises more than one angiogenesis inhibitor.

16. The composition of claim 15, wherein at least one angiogenesis inhibitor has an effective average particle size which is greater than about 2 microns.

17. The composition of claim 1, additionally comprising at least one nanoparticulate angiogenesis inhibitor composition having an effective average particle size of less than about 2 microns, wherein said additional nanoparticulate angiogenesis inhibitor composition has an effective average particle size which is different than the particle size of the nanoparticulate angiogenesis inhibitor composition of claim 1.

18. The composition of claim 1, additionally comprising at least one non-angiogenesis inhibitor active agent.

19. The composition of claim 18, wherein said active agent is selected from the group consisting of amino acids, proteins, peptides, nucleotides, anti-obesity drugs, nutraceuticals, dietary supplements, central nervous symptom stimulants, carotenoids, corticosteroids, elastase inhibitors, anti-fungals, alkylxanthine, oncology therapies, anti-emetics, analgesics, opioids, antipyretics, cardiovascular agents, anti-inflammatory agents, anthelmintics, anti-arrhythmic agents, antibiotics, anticoagulants, antidepressants, antidiabetic agents, antiepileptics, antihistamines, antihypertensive agents, antimuscarinic agents, antimycobacterial agents, antineoplastic agents, immunosuppressants, antithyroid agents, antiviral agents, anxiolytics, sedatives, astringents, alpha-adrenergic receptor blocking agents, beta-adrenoceptor blocking agents, blood products, blood substitutes, cardiac inotropic agents, contrast media, corticosteroids, cough suppressants, diagnostic agents, diagnostic imaging agents, diuretics, dopaminergics, haemostatics, immunological agents, lipid regulating agents, muscle relaxants, parasympathomimetics, parathyroid calcitonin and biphosphonates, prostaglandins, radio-pharmaceuticals, sex hormones,

anti-allergic agents, stimulants, anoretics, sympathomimetics, thyroid agents, vasodilators, vasomodulator, xanthines, Mu receptor antagonists, Kappa receptor antagonists, non-narcotic analgesics, monoamine uptake inhibitors, adenosine regulating agents, cannabinoid derivatives, Substance P antagonists, neurokinin-1 receptor antagonists, and sodium channel blockers.

20. The composition of claim 19, wherein said nutraceutical is selected from the group consisting of lutein, folic acid, fatty acids, fruit extracts, vegetable extracts, vitamin supplements, mineral supplements, phosphatidylserine, lipoic acid, melatonin, glucosamine/chondroitin, Aloe Vera, Guggul, glutamine, amino acids, green tea, lycopene, whole foods, food additives, herbs, phytonutrients, antioxidants, flavonoid constituents of fruits, evening primrose oil, flax seeds, fish oils, marine animal oils, and probiotics.

21. The composition of any of claims 20, 21, or 22, wherein at least one non-angiogenesis inhibitor active agent has an effective average particle size of less than about 2 microns.

22. The composition of any of any of claims 20, 21, or 22, wherein at least one non-angiogenesis inhibitor active agent has an effective average particle size of greater than about 2 microns.

23. The composition of claim 1, wherein upon administration the composition redisperses such that the angiogenesis inhibitor particles have a particle size selected from the group consisting of less than about 2 microns, less than about 1900 nm, less than about 1800 nm, less than about 1700 nm, less than about 1600 nm, less than about 1500 nm, less than about 1400 nm, less than about 1300 nm, less than about 1200 nm, less than about 1100 nm, less than about 1000 nm, less than about 900 nm, less than about 800 nm, less than about 700 nm, less than about 600 nm, less than about 500 nm, less than about 400 nm, less than about 300 nm, less than about 250 nm, less than about 200 nm, less than about 150 nm, less than about 100 nm, less than about 75 nm, and less than about 50 nm.

24. The composition of claim 1, wherein the composition does not produce significantly different absorption levels when administered under fed as compared to fasting conditions.

25. The composition of claim 1, wherein the difference in absorption of the nanoparticulate angiogenesis inhibitor composition of the invention, when administered in the fed versus the fasted state, is selected from the group consisting of less than about 100%, less than about 90%, less than about 80%, less than about 70%, less than about 60%, less than about 50%, less than about 40%, less than about 35%, less than about 30%, less than about 25%, less than about 20%, less than about 15%, less than about 10%, less than about 5%, and less than about 3%.

26. The composition of claim 1, wherein the composition does not produce significantly different rates of absorption (T_{\max}) when administered under fed as compared to fasting conditions.

27. The composition of claim 1, wherein the difference in the T_{\max} for the nanoparticulate angiogenesis inhibitor composition of the invention, when administered in the fed versus the fasted state, is less than about 100%, less than about 90%, less than about 80%, less than about 70%, less than about 60%, less than about 50%, less than about 40%, less than about 30%, less than about 20%, less than about 15%, less than about 10%, less than about 5%, and less than about 3%.

28. The composition of claim 1, wherein upon administration the T_{\max} is less than that of a conventional non-nanoparticulate composition of the same angiogenesis inhibitor, administered at the same dosage.

29. The composition of claim 1, wherein in comparative pharmacokinetic testing with a non-nanoparticulate composition of the same angiogenesis inhibitor, administered at the same dosage, the nanoparticulate composition exhibits a T_{\max} selected from the group consisting of less than about 100%, less than about 90%, less than about 80%, less than about 70%, less than about 60%, less than about 50%, less than about 40%, less than about 30%, less than about 25%, less than about 20%, less than about 15%, and less than about 10% of the T_{\max} exhibited by the non-nanoparticulate composition of the angiogenesis inhibitor.

30. The composition of claim 1, wherein following administration the composition has a T_{\max} selected from the group consisting of less than about 2.5 hours, less than about 2.25 hours, less than about 2 hours, less than about 1.75 hours, less than about 1.5 hours, less than about 1.25 hours, less than about 1.0 hours, less than about 50 minutes, less than about 40 minutes, less than about 30 minutes, less than about 25 minutes, less than about 20 minutes, less than about 15 minutes, and less than about 10 minutes.

31. The composition of claim 1, wherein upon administration the C_{\max} of the composition is greater than the C_{\max} of a conventional non-nanoparticulate composition of the same angiogenesis inhibitor, administered at the same dosage.

32. The composition of claim 1, wherein in comparative pharmacokinetic testing with a non-nanoparticulate composition of the same angiogenesis inhibitor, administered at the same dosage, the nanoparticulate composition exhibits a C_{\max} selected from the group consisting of greater than about 5%, greater than about 10%, greater than about 15%, greater than about 20%, greater than about 30%, greater than about 40%, greater than about 50%, greater than about 60%, greater than about 70%, greater than about 80%, greater than about 90%, greater than about 100%, greater than about 110%, greater than about 120%, greater than about 130%, greater than about 140%, and greater than about 150% than the C_{\max} exhibited by the non-nanoparticulate composition of the angiogenesis inhibitor.

AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions of claims in the application.

1. (Original) A statin composition comprising:
 - (a) particles of at least one statin or a salt thereof, wherein the particles have an effective average particle size of less than about 2000 nm; and
 - (b) at least one surface stabilizer.
2. (Currently Amended) The composition of claim 1, wherein the statin is selected from the group consisting of atorvastatin; a 6-[2-(substituted-pyrrol-1-yl)alkyl]pyran-2-ones and derivative other than atorvastatin; lovastatin; a keto analog of mevinolin other than lovastatin; pravastatin; simvastatin; velostatin; fluindostatin; pyrazole analogs of mevalonolactone derivatives; rivastatin; a pyridyldihydroxyheptenoic acid other than rivastatin; SC-45355; dichloroacetate; imidazole analogs of mevalonolactone; 3-carboxy-2-hydroxy-propane-phosphonic acid derivatives; 2,3-di-substituted pyrrole derivatives; 2,3-di-substituted furan derivatives; 2,3-di-substituted thiophene derivatives; naphthyl analogs of mevalonolactone; octahydronaphthalenes; and phosphinic acid compounds.
3. (Original) The composition of claim 1, wherein the statin is lovastatin or simvastatin.
4. (Currently Amended) The composition of claim 1, wherein the statin is selected from the group consisting of a crystalline phase, an amorphous phase, and a semi-crystalline phase, ~~a semi-amorphous phase, and mixtures thereof.~~
5. (Original) The composition of claim 1, wherein the effective average particle size of the statin particles is selected from the group consisting of less than about 1900 nm, less than about 1800 nm, less than about 1700 nm, less than about 1600 nm, less than about 1500 nm, less than about 1400 nm, less than about 1300 nm, less than about 1200 nm, less than about 1100 nm, less than about 1000 nm, less than about 900 nm, less than about 800 nm, less than about 700 nm, less than about 600 nm, less than about 500 nm, less than about

400 nm, less than about 300 nm, less than about 250 nm, less than about 200 nm, less than about 100 nm, less than about 75 nm, and less than about 50 nm.

6. (Previously Presented) The composition of claim 1, wherein the composition is formulated:

(a) for administration selected from the group consisting of oral, pulmonary, rectal, ophthalmic, colonic, parenteral, intracisternal, intravaginal, intraperitoneal, local, buccal, nasal, and topical administration;

(b) into a dosage form selected from the group consisting of liquid dispersions, oral suspensions, gels, aerosols, ointments, creams, tablets, capsules;

(c) into a dosage form selected from the group consisting of controlled release formulations, fast melt formulations, lyophilized formulations, delayed release formulations, extended release formulations, pulsatile release formulations, and mixed immediate release and controlled release formulations; or

(d) a combination thereof.

7. (Cancelled)

8. (Original) The composition of claim 1, wherein the composition further comprises one or more pharmaceutically acceptable excipients, carriers, or a combination thereof.

9. (Previously Presented) The composition of claim 1, wherein:

(a) the at least one statin or a salt thereof is present in an amount selected from the group consisting of from about 99.5% to about 0.001%, from about 95% to about 0.1%, and from about 90% to about 0.5%, by weight, based on the total combined weight of the statin or a salt thereof and at least one surface stabilizer, not including other excipients;

(b) the at least one surface stabilizer is present in an amount selected from the group consisting of from about 0.5% to about 99.999% by weight, from about 5.0% to about 99.9% by weight, and from about 10% to about 99.5% by weight, based on the total combined dry weight of the statin or a salt thereof and at least one surface stabilizer, not

including other excipients; or

(c) a combination thereof.

10. (Cancelled)

11. (Original) The composition of claim 1, comprising at least one primary surface stabilizer and at least one secondary surface stabilizer.

12. (Previously Presented) The composition of claim 1, wherein the surface stabilizer is selected from the group consisting of a nonionic surface stabilizer, an anionic surface stabilizer, a cationic surface stabilizer, a zwitterionic surface stabilizer, and an ionic surface stabilizer.

13. (Currently Amended) The composition of claim 1, wherein the at least one surface stabilizer is selected from the group consisting of cetyl pyridinium chloride, gelatin, casein, phosphatides, dextran, glycerol, gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glycerol monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers, polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters, polyethylene glycols, dodecyl trimethyl ammonium bromide, polyoxyethylene stearates, colloidal silicon dioxide, phosphates, sodium dodecylsulfate, carboxymethylcellulose calcium, hydroxypropyl celluloses, hypromellose, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hypromellose phthalate, noncrystalline cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol, polyvinylpyrrolidone, 4-(1,1,3,3-tetramethylbutyl)-phenol polymer with ethylene oxide and formaldehyde, poloxamers; poloxamines, a charged phospholipid, dioctylsulfosuccinate, dialkylesters of sodium sulfosuccinic acid, sodium lauryl sulfate, alkyl aryl polyether sulfonates, mixtures of sucrose stearate and sucrose distearate, p-isononylphenoxypoly-(glycidol), decanoyl-N-methylglucamide; n-decyl β -D-glucopyranoside; n-decyl β -D-maltopyranoside; n-dodecyl β -D-glucopyranoside; n-dodecyl β -D-maltoside; heptanoyl-N-methylglucamide; n-heptyl- β -D-glucopyranoside; n-heptyl β -D-thioglucoside; n-hexyl β -D-glucopyranoside; nonanoyl-N-methylglucamide; n-nonyl β -D-glucopyranoside; octanoyl-N-methylglucamide; n-octyl- β -D-glucopyranoside; octyl β -D-thioglucopyranoside;

lysozyme, PEG-phospholipid, PEG-cholesterol, PEG-cholesterol derivative, PEG-vitamin A, lysozyme, random copolymers of vinyl acetate and vinyl pyrrolidone, a cationic polymer, a cationic biopolymer, a cationic polysaccharide, a cationic cellulosic, a cationic alginate, a cationic nonpolymeric compound, a cationic phospholipid, cationic lipids, polymethylmethacrylate trimethylammonium bromide, sulfonium compounds, polyvinylpyrrolidone-2-dimethylaminoethyl methacrylate dimethyl sulfate, hexadecyltrimethyl ammonium bromide, phosphonium compounds, quarternary ammonium compounds, benzyl-di(2-chloroethyl)ethylammonium bromide, coconut trimethyl ammonium chloride, coconut trimethyl ammonium bromide, coconut methyl dihydroxyethyl ammonium chloride, coconut methyl dihydroxyethyl ammonium bromide, decyl triethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride bromide, C₁₂₋₁₅dimethyl hydroxyethyl ammonium chloride, C₁₂₋₁₅dimethyl hydroxyethyl ammonium chloride bromide, coconut dimethyl hydroxyethyl ammonium chloride, coconut dimethyl hydroxyethyl ammonium bromide, myristyl trimethyl ammonium methyl sulphate, lauryl dimethyl benzyl ammonium chloride, lauryl dimethyl benzyl ammonium bromide, lauryl dimethyl (ethenoxy)₄ ammonium chloride, lauryl dimethyl (ethenoxy)₄ ammonium bromide, N-alkyl (C₁₂₋₁₈)dimethylbenzyl ammonium chloride, N-alkyl (C₁₄₋₁₈)dimethyl-benzyl ammonium chloride, N-tetradecyldimethylbenzyl ammonium chloride monohydrate, dimethyl didecyl ammonium chloride, N-alkyl and (C₁₂₋₁₄) dimethyl 1-naphthylmethyl ammonium chloride, trimethylammonium halide, alkyl-trimethylammonium salts, dialkyl-dimethylammonium salts, lauryl trimethyl ammonium chloride, ethoxylated alkyamidoalkyldialkylammonium salt, an ethoxylated trialkyl ammonium salt, dialkylbenzene dialkylammonium chloride, N-didecyldimethyl ammonium chloride, N-tetradecyldimethylbenzyl ammonium, chloride monohydrate, N-alkyl(C₁₂₋₁₄) dimethyl 1-naphthylmethyl ammonium chloride, dodecyldimethylbenzyl ammonium chloride, dialkyl benzenealkyl ammonium chloride, lauryl trimethyl ammonium chloride, alkylbenzyl methyl ammonium chloride, alkyl benzyl dimethyl ammonium bromide, C₁₂ trimethyl ammonium bromides, C₁₅ trimethyl ammonium bromides, C₁₇ trimethyl ammonium bromides, dodecylbenzyl triethyl ammonium chloride, poly-diallyldimethylammonium chloride (DADMAC), dimethyl ammonium chlorides, alkyl dimethylammonium halogenides, tricetyl methyl ammonium chloride,

decyltrimethylammonium bromide, dodecyltriethylammonium bromide, tetradecyltrimethylammonium bromide, methyl trioctylammonium chloride, ~~POLYQUAT-10™~~ polyquaternium 10, tetrabutylammonium bromide, benzyl trimethylammonium bromide, choline esters, benzalkonium chloride, stearylalkonium chloride compounds, cetyl pyridinium bromide, cetyl pyridinium chloride, halide salts of quaternized polyoxyethylalkylamines, ~~MIRAPOL™, ALKAQUAT™~~ quaternized ammonium salt polymers, alkyl pyridinium salts; amines, amine salts, amine oxides, imide azolinium salts, protonated quaternary acrylamides, methylated quaternary polymers, and cationic guar.

14.-17. (Cancelled)

18. (Previously Presented) The composition of claim 1, wherein:

- (a) the T_{max} of the statin, when assayed in the plasma of a mammalian subject following administration, is less than the T_{max} for a conventional, non-nanoparticulate form of the same statin, administered at the same dosage;
- (b) the C_{max} of the statin, when assayed in the plasma of a mammalian subject following administration, is greater than the C_{max} for a conventional, non-nanoparticulate form of the same statin, administered at the same dosage;
- (c) the AUC of the statin, when assayed in the plasma of a mammalian subject following administration, is greater than the AUC for a conventional, non-nanoparticulate form of the same statin, administered at the same dosage; or
- (d) a combination thereof.

19. (Previously Presented) The composition of claim 18, wherein:

- (a) the T_{max} is selected from the group consisting of not greater than about 90%, not greater than about 80%, not greater than about 70%, not greater than about 60%, not greater than about 50%, not greater than about 30%, not greater than about 25%, not greater than about 20%, not greater than about 15%, and not greater than about 10% of the T_{max} , exhibited by a non-nanoparticulate formulation of the same statin, administered at the same dosage;
- (b) the C_{max} is selected from the group consisting of at least about 10%, at least

about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, and at least about 100% greater than the C_{\max} exhibited by a non-nanoparticulate formulation of the same statin, administered at the same dosage;

(c) the AUC is selected from the group consisting of at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, and at least about 100% greater than the AUC exhibited by a non-nanoparticulate formulation of the same statin, administered at the same dosage; or

(d) a combination thereof.

20.-23. (Cancelled)

24. (Original) The composition of claim 1 which does not produce significantly different absorption levels when administered under fed as compared to fasting conditions.

25. (Original) The composition of claim 24, wherein the difference in absorption of the statin composition of the invention, when administered in the fed versus the fasted state, is selected from the group consisting of less than about 100%, less than about 90%, less than about 80%, less than about 70%, less than about 60%, less than about 50%, less than about 40%, less than about 30%, less than about 25%, less than about 20%, less than about 15%, less than about 10%, less than about 5%, and less than about 3%.

26. (Original) The composition of claim 1, wherein administration of the composition to a subject in a fasted state is bioequivalent to administration of the composition to a subject in a fed state, when administered to a human.

27. (Previously Presented) The composition of claim 26, wherein "bioequivalency" is established by:

(a) a 90% Confidence Interval of between 0.80 and 1.25 for both C_{\max} and AUC, when administered to a human; or

(b) a 90% Confidence Interval of between 0.80 and 1.25 for AUC and a 90% Confidence Interval of between 0.70 to 1.43 for C_{max} , when administered to a human.

28. (Cancelled)

29. (Previously Presented) The composition of claim 1, wherein:

(a) within about 5 minutes at least about 20%, at least about 30%, or at least about 40% of the composition is dissolved;

(b) within about 10 minutes at least about 40%, at least about 50%, about 60%, about 70%, or about 80% of the composition is dissolved;

(c) within about 20 minutes at least about 70%, at least about 80%, about 90%, or about 100% of the composition is dissolved,

wherein dissolution is measured in a media which is discriminating and wherein the rotating blade method (European Pharmacopoeia) is used to measure dissolution, wherein dissolution is measured in a media which is discriminating and wherein the rotating blade method (European Pharmacopoeia) is used to measure dissolution.

30.-36. (Cancelled)

37. (Previously Presented) The composition of claim 29, wherein upon redispersion the statin particles have an effective average particle size of less than about 2 microns.

38. (Previously Presented) The composition of claim 1, additionally comprising one or more non-statin active agents selected from the group consisting of:

- (a) an active agent useful in treating dyslipidemia;
- (b) an active agent useful in treating hyperlipidemia;
- (c) an active agent useful in treating hypercholesterolemia;
- (d) an active agent useful in treating cardiovascular disorders;
- (e) an active agent useful in treating hypertriglyceridemia;
- (f) an active agent useful in treating coronary heart disease;
- (g) an active agent useful in treating peripheral vascular disease;

(h) an active agent useful as adjunctive therapy to diet for the reduction of LDL-C, total-C, triglycerides, and/or Apo B in adult patients with primary hypercholesterolemia or mixed dyslipidemia (Fredrickson Types IIa and IIb);

(i) an active agent useful as adjunctive therapy to diet for treatment of adult patients with hypertriglyceridemia (Fredrickson Types IV and V hyperlipidemia);

(j) an active agent useful in treating pancreatitis;

(k) an active agent useful in treating restenosis;

(l) an active agent useful in treating Alzheimer's disease;

(m) cholesterol lowering agents;

(n) polycosanols;

(o) alkanoyl L-carnitines,

(p) antihypertensives, and

(q) sterols and/or stanols.

39. (Cancelled)

40. (Previously Presented) The composition of claim 38, wherein:

(a) the cholesterol lowering agent is selected from the group consisting of ACE inhibitors, nicotinic acid, niacin, bile acid sequestrants, fibrates, vitamins, fatty acid derivatives, long chain plant extract alcohols, ezetimibe, and celluloses;

(b) the polycosanol is selected from the group consisting of (1) triacontanol, (2) hexacontanol, (3) ecocosanol, (4) hexacosanol, (5) tetracosanol, (6) dotriacontanol, (7) tetracontanol, (8) natural products comprising triacontanol, hexacontanol, ecocosanol, hexacosanol, tetracosanol, dotriacontanol, or tetracontanol; and (9) extracts of natural products comprising triacontanol, hexacontanol, ecocosanol, hexacosanol, tetracosanol, dotriacontanol, or tetracontanol;

(c) the antihypertensive is selected from the group consisting of diuretics, beta blockers, alpha blockers, alpha-beta blockers, sympathetic nerve inhibitors, angiotensin converting enzyme (ACE) inhibitors, calcium channel blockers, and angiotensin receptor blockers; or

(d) the sterol is selected from the group consisting of plant sterols, plant sterol

esters, sitosterol, sitostanol, fish oil, phytosterol, campestanol, stigmasterol, coprostanol, cholestanol, and beta-sitosterol.

41.-43. (Cancelled)

44. (Previously Presented) The composition according to claim 40, wherein:

(a) at least one of the non-statin compounds has an effective average particle size of greater than about 2 microns; or

(b) at least one of the non-statin compounds has an effective average particle size of less than about 2 microns.

45. (Cancelled).

46. (Previously Presented) The composition of claim 1, wherein:

(a) upon administration the composition redisperses such that the statin particles have an effective average particle size selected from the group consisting of less than about 2000 nm, less than about 1900 nm, less than about 1800 nm, less than about 1700 nm, less than about 1600 nm, less than about 1500 nm, less than about 1400 nm, less than about 1300 nm, less than about 1200 nm, less than about 1100 nm, less than about 1000 nm, less than about 900 nm, less than about 800 nm, less than about 700 nm, less than about 600 nm, less than about 500 nm, less than about 400 nm, less than about 300 nm, less than about 250 nm, less than about 200 nm, less than about 150 nm, less than about 100 nm, less than about 75 nm, and less than about 50 nm;

(b) the composition redisperses in a biorelevant media such that the statin particles have an effective average particle size selected from the group consisting of less than about 2 microns, less than about 1900 nm, less than about 1800 nm, less than about 1700 nm, less than about 1600 nm, less than about 1500 nm, less than about 1400 nm, less than about 1300 nm, less than about 1200 nm, less than about 1100 nm, less than about 1000 nm, less than about 900 nm, less than about 800 nm, less than about 700 nm, less than about 600 nm, less than about 500 nm, less than about 400 nm, less than about 300 nm, less than about 250 nm, less than about 200 nm, less than about 150 nm, less than about 100 nm, less than about 75 nm,

and less than about 50 nm; or

(c) a combination thereof.

47. (Cancelled)

48. (Original) A method of making a statin composition comprising contacting particles of at least one statin or a salt thereof with at least one surface stabilizer for a time and under conditions sufficient to provide a statin composition having an effective average particle size of less than about 2000 nm.

49. (Previously Presented) The method of claim 48, wherein said contacting comprises grinding, wet grinding, homogenizing, precipitation, or a combination thereof.

50.-52. (Cancelled)

53. (Original) The method of claim 48, wherein the statin is selected from the group consisting of atorvastatin; a 6-[2-(substituted-pyrrol-1-yl)alkyl]pyran-2-ones and derivative other than atorvastatin; lovastatin; a keto analog of mevinolin other than lovastatin; pravastatin; simvastatin; velostatin; fluindostatin; pyrazole analogs of mevalonolactone derivatives; rivastatin; a pyridyldihydroxyheptenoic acid other than rivastatin; SC-45355; dichloroacetate; imidazole analogs of mevalonolactone; 3-carboxy-2-hydroxy-propane-phosphonic acid derivatives; 2,3-di-substituted pyrrole derivatives; 2,3-di-substituted furan derivatives; 2,3-di-substituted thiophene derivatives; naphthyl analogs of mevalonolactone; octahydronaphthalenes; phosphinic acid compounds.

54. (Original) The method of claim 48, wherein the statin is lovastatin or simvastatin.

55. (Cancelled)

56. (Original) The method of claim 48, wherein the effective average particle size of the statin particles is selected from the group consisting of less than about 1900 nm, less than about 1800 nm, less than about 1700 nm, less than about 1600 nm, less than about 1500 nm, less than about 1000 nm, less than about 1400 nm, less than about 1300 nm, less than

about 1200 nm, less than about 1100 nm, less than about 900 nm, less than about 800 nm, less than about 700 nm, less than about 600 nm, less than about 500 nm, less than about 400 nm, less than about 300 nm, less than about 250 nm, less than about 200 nm, less than about 100 nm, less than about 75 nm, and less than about 50 nm.

57.-67. (Cancelled)

68. (Currently Amended) A method of treating a subject ~~in need~~ who suffers from hypercholesterolemia, hypertriglyceridemia, coronary heart disease, or peripheral vascular disease, comprising administering to the subject an effective amount of a composition comprising:

- (a) particles of a statin or a salt thereof, wherein the statin particles have an effective average particle size of less than about 2000 nm; and
- (b) at least one surface stabilizer associated with the surface of the statin particles.

69. (Original) The method of claim 68, wherein the statin is selected from the group consisting of atorvastatin; a 6-[2-(substituted-pyrrol-1-yl)alkyl]pyran-2-ones and derivative other than atorvastatin; lovastatin; a keto analog of mevinolin other than lovastatin; pravastatin; simvastatin; velostatin; fluindostatin; pyrazole analogs of mevalonolactone derivatives; rivastatin; a pyridyldihydroxyheptenoic acid other than rivastatin; SC-45355; dichloroacetate; imidazole analogs of mevalonolactone; 3-carboxy-2-hydroxy-propane-phosphonic acid derivatives; 2,3-di-substituted pyrrole derivatives; 2,3-di-substituted furan derivatives; 2,3-di-substituted thiophene derivatives; naphthyl analogs of mevalonolactone; octahydronaphthalenes; phosphinic acid compounds.

70. (Original) The method of claim 68, wherein the statin is lovastatin or simvastatin.

71. (Cancelled)

72. (Original) The method of claim 68, wherein the effective average particle size of the statin particles is selected from the group consisting of less than about 1900 nm, less than about 1800 nm, less than about 1700 nm, less than about 1600 nm, less than about 1500

nm, less than about 1400 nm, less than about 1300 nm, less than about 1200 nm, less than about 1100 nm, less than about 1000 nm, less than about 900 nm, less than about 800 nm, less than about 700 nm, less than about 600 nm, less than about 500 nm, less than about 400 nm, less than about 300 nm, less than about 250 nm, less than about 200 nm, less than about 100 nm, less than about 75 nm, and less than about 50 nm.

73.-95. (Cancelled)

96. (Previously Presented) The method of claim 68, additionally comprising administering one or more non-statin active agents selected from the group consisting of:

- (a) an active agent useful in treating dyslipidemia;
- (b) an active agent useful in treating hyperlipidemia;
- (c) an active agent useful in treating hypercholesterolemia;
- (d) an active agent useful in treating cardiovascular disorders;
- (e) an active agent useful in treating hypertriglyceridemia;
- (f) an active agent useful in treating coronary heart disease;
- (g) an active agent useful in treating peripheral vascular disease;
- (h) an active agent useful as adjunctive therapy to diet for the reduction of LDL-C, total-C, triglycerides, and/or Apo B in adult patients with primary hypercholesterolemia or mixed dyslipidemia (Fredrickson Types IIa and IIb);
- (i) an active agent useful as adjunctive therapy to diet for treatment of adult patients with hypertriglyceridemia (Fredrickson Types IV and V hyperlipidemia);
- (j) an active agent useful in treating pancreatitis;
- (k) an active agent useful in treating restenosis;
- (l) an active agent useful in treating Alzheimer's disease;
- (m) cholesterol lowering agents;
- (n) polycosanols;
- (o) alkanoyl L-carnitines;
- (p) antihypertensives; and
- (q) sterols and/or stanols.

97. (Cancelled)

98. (Previously Presented) The method of claim 96, wherein:

(a) the cholesterol lowering agent is selected from the group consisting of ACE inhibitors, nicotinic acid, niacin, bile acid sequestrants, fibrates, vitamins, fatty acid derivatives, long chain plant extract alcohols, ezetimibe, and celluloses;

(b) the polycosanol is selected from the group consisting of (1) triacontanol, (2) hexacontanol, (3) ecocosanol, (4) hexacosanol, (5) tetracosanol, (6) dotriacontanol, (7) tetracontanol, (8) natural products comprising triacontanol, hexacontanol, ecocosanol, hexacosanol, tetracosanol, dotriacontanol, or tetracontanol; and (9) extracts of natural products comprising triacontanol, hexacontanol, ecocosanol, hexacosanol, tetracosanol, dotriacontanol, or tetracontanol;

(c) the antihypertensive is selected from the group consisting of diuretics, beta blockers, alpha blockers, alpha-beta blockers, sympathetic nerve inhibitors, angiotensin converting enzyme (ACE) inhibitors, calcium channel blockers, and angiotensin receptor blockers; or

(d) the sterol and/or stanol is selected from the group consisting of plant sterols, plant sterol esters, sitosterol, sitostanol, fish oil, phytosterol, campestanol, stigmasterol, coprostanol, cholestanol, and beta-sitosterol.

99.-101. (Cancelled)

102. (Original) The method of claim 68, wherein the subject is a human.

103. (Previously Presented) The method of claim 68, wherein the method is used:

(a) to treat a condition selected from the group consisting of hypercholesterolemia, hypertriglyceridemia, coronary heart disease, cardiovascular disorders, and peripheral vascular disease;

(b) as adjunctive therapy to diet for the reduction of LDL-C, total-C, triglycerides, or Apo B in adult patients with primary hypercholesterolemia or mixed dyslipidemia;

(c) as adjunctive therapy to diet for treatment of adult patients with hypertriglyceridemia;

- (d) to decrease the risk of pancreatitis;
- (e) to decrease the risk of or to treat Alzheimer's disease;
- (f) to treat indications where lipid regulating agents are typically used; or
- (g) a combination thereof.

104.-108. (Cancelled)

AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions of claims in the application.

1. (Currently Amended) A ~~stable meloxicam nanoparticulate composition~~ pharmaceutical dosage form suitable for intravenous injection comprising:
 - (a) a liquid dispersion medium;
 - (b) particles of meloxicam or a salt thereof having an effective average particle size of less than about 2000 nm; and
 - (b) (c) at least one polyvinylpyrrolidone, sodium deoxycholate, or a combination of polyvinylpyrrolidone and sodium deoxycholate as surface stabilizers adsorbed on the surface of the meloxicam particles, wherein the surface stabilizer is essentially free of intermolecular cross-linkages;

~~wherein in comparative pharmacokinetic testing with a non-nanoparticulate formulation of meloxicam having the same dosage strength and form, the composition exhibits a shorter time to T_{max} when compared to the time to T_{max} of the non-nanoparticulate meloxicam formulation.~~
2. (Currently Amended) The ~~composition~~ pharmaceutical dosage form of claim 1, wherein the meloxicam is selected from the group consisting of a crystalline phase, an amorphous phase, and a semi-crystalline phase.
3. (Currently Amended) The ~~composition~~ pharmaceutical dosage form of claim 1, wherein the effective average particle size of the nanoparticulate meloxicam particles is selected from the group consisting of less than about 1500 nm, less than about 1000 nm, less than about 900 nm, less than about 800 nm, less than about 700 nm, less than about 600 nm, less than about 500 nm, less than about 400 nm, less than about 300 nm, less than about 250 nm, less than about 200 nm, less than about 100 nm, less than about 75 nm, and less than about 50 nm.
- 4.-5. (Cancelled)

6. (Currently Amended) The ~~composition~~ pharmaceutical dosage form of claim 1, wherein the ~~composition~~ pharmaceutical dosage form further comprises one or more pharmaceutically acceptable excipients, carriers, or a combination thereof.

7. (Currently Amended) The ~~composition~~ pharmaceutical dosage form of claim 1, wherein the meloxicam is present in an amount selected from the group consisting of from ~~about~~ 99.5% to ~~about~~ 0.001%, from ~~about~~ 95% to ~~about~~ 0.1%, and from ~~about~~ 90% to ~~about~~ 0.5%, by weight, based on the total combined weight of the meloxicam and at least one surface stabilizer, not including other excipients.

8. (Currently Amended) The ~~composition~~ pharmaceutical dosage form of claim 1, wherein the ~~at least one~~ surface stabilizer is present in an amount selected from the group consisting of from ~~about~~ 0.01% to ~~about~~ 99.5% by weight, from ~~about~~ 0.1% to ~~about~~ 95% by weight, and from ~~about~~ 0.5% to ~~about~~ 90% by weight, based on the total combined dry weight of meloxicam and at least one surface stabilizer, not including other excipients.

9.-15. (Cancelled)

16. (Currently Amended) The ~~composition~~ pharmaceutical dosage form of claim 1, wherein the C_{\max} of the ~~composition~~ pharmaceutical dosage form, when assayed in the plasma of the mammalian subject, is selected from the group consisting of greater than ~~about~~ 1 g/mL, greater than ~~about~~ 3 g/mL, greater than ~~about~~ 5 g/mL, greater than ~~about~~ 10 g/mL, and greater than ~~about~~ 15 g/mL.

17. (Cancelled)

18. (Currently Amended) The ~~composition~~ pharmaceutical dosage form of claim 1, additionally comprising a meloxicam composition having an effective average particle size which is greater than ~~about~~ 2 microns.

19. (Currently Amended) The ~~composition~~ pharmaceutical dosage form of claim 1, additionally comprising at least one additional nanoparticulate meloxicam composition, having an effective average particle size of less than ~~about~~ 2 microns, wherein said additional nanoparticulate meloxicam composition has an effective average particle size which is different than particle size of the ~~nanoparticulate meloxicam composition~~ pharmaceutical dosage form of claim 1.

20. (Currently Amended) The ~~composition~~ pharmaceutical dosage form of claim 1, additionally comprising at least one non-meloxicam active agent selected from the group consisting of proteins, peptides, nucleotides, anti-obesity drugs, nutraceuticals, dietary supplements, carotenoids, corticosteroids, elastase inhibitors, anti-fungals, alkylxanthine, oncology therapies, anti-emetics, analgesics, opioids, antipyretics, cardiovascular agents, anti-inflammatory agents, anthelmintics, anti-arrhythmic agents, antibiotics, anticoagulants, antidepressants, antidiabetic agents, antiepileptics, antihistamines, antihypertensive agents, antimuscarinic agents, antimycobacterial agents, antineoplastic agents, immunosuppressants, antithyroid agents, antiviral agents, anxiolytics, sedatives, astringents, beta-adrenoceptor blocking agents, blood products, blood substitutes, cardiac inotropic agents, contrast media, corticosteroids, cough suppressants, diagnostic agents, diagnostic imaging agents, diuretics, dopaminergics, haemostatics, immunological agents, lipid regulating agents, muscle relaxants, parasympathomimetics, parathyroid calcitonin and biphosphonates, prostaglandins, radio-pharmaceuticals, sex hormones, anti-allergic agents, stimulants, anoretics, sympathomimetics, thyroid agents, Mu receptor antagonists, Kappa receptor antagonists, non-narcotic analgesics, monoamine uptake inhibitors, adenosine regulating agents, cannabinoid derivatives, Substance P antagonists, neurokinin-1 receptor antagonists, and sodium channel blockers.

21. (Currently Amended) The ~~composition~~ pharmaceutical dosage form of claim 20, wherein said nutraceutical is selected from the group consisting of lutein, folic acid, fatty acids, fruit extracts, vegetable extracts, vitamin supplements, mineral supplements, phosphatidylserine,

lipoic acid, melatonin, glucosamine/chondroitin, Aloe Vera, Guggul, glutamine, amino acids, green tea, lycopene, whole foods, food additives, herbs, phytonutrients, antioxidants, flavonoid constituents of fruits, evening primrose oil, flax seeds, fish oils, marine animal oils, and probiotics.

22. (Currently Amended) The ~~composition~~ pharmaceutical dosage form of claim 20, wherein said anti-inflammatory agent is a COX-2 inhibitor selected from the group consisting of celecoxib, rofecoxib, valdecoxib, parecoxib, MK-966, etoricoxib, 4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]] benzenesulfonamide, N-(2-cyclohexyloxy-4-nitrophenyl)methane sulfonamide, methyl sulfone spiro(2.4)hept-5-ene 1, SC-57666, celexcoxib, SC-558, SC-560, etodolac, 5,5-dimethyl-3-(3-fluorophenyl)-4-(4-methylsulfonyl)phenyl 2(5H)-furanone, MK-476, L-745337, L-761066, L-761000, L-748780, L-748731, 5-Bromo-2-(4-fluorophenyl)-3-(4-(methylsulfonyl)phenyl, 1-(7-tert.-butyl-2,3-dihydro-3,3-dimethylbenzo(b)furan-5-yl)-4-cyclopropylbutan-1-one, 3-formylamino-7-methylsulfonylamino-6-phenoxy-4H-1-benzopyran-4-one, BF 389, PD 136005, PD 142893, PD 145065, flurbiprofen, nimesulide, nabumetone, flosulide, piroxicam, dicofenac, COX-189, D 1367, 4 nitro 2-phenoxy-methane sulfonanilide, (3-benzoyldifluoromethane sulfonanilide, diflumidone), JTE-522, 4'-Acetyl-2'-(2,4-difluorophenoxy)methanesulfonanilide, FK 867, FR 115068, GR 253035, RWJ 63556, RWJ 20485, ZK 38997, (E)-(5)-(3,5-di-tert-butyl-4-hydroxybenzylidene)-2-ethyl-1,2-isothiazolidine-1,1-dioxide indomethacin, CL 1004, RS 57067, RS 104894, SC 41930, SB 205312, SKB 209670, and Ono 1078.

23. (Currently Amended) The ~~composition~~ pharmaceutical dosage form of claim 20, wherein said non-meloxicam active agent is selected from the group consisting of aceclofenac, acetaminophen, e-acetamidocaproic acid, acetaminophen, acetaminosalol, acetanilide, acetylsalicylic acid, S-adenosylmethionine, alclofenac, alfentanil, allylprodine, alminoprofen, aloxiprin, alphaprodine, aluminum bis(acetylsalicylate), amfenac, aminochlorthenoxazin, 3-amino-4-hydroxybutyric acid, 2-amino-4-picoline, aminopropylon, aminopyrine, amixetrine, ammonium

salicylate, ampiroxicam, amtolmetin guacil, anileridine, antipyrine, antipyrine salicylate, antrafenine, apazone, bendazac, benorylate, benoxaprofen, benzpiperylon, benzydamine, benzylmorphine, bermoprofen, bezitramide, -bisabolol, bromfenac, p-bromoacetanilide, 5-bromosalicylic acid acetate, bromosaligenin, bucetin, bucloxic acid, bucolome, bufexamac, bumadizon, buprenorphine, butacetin, butibufen, butophanol, calcium acetylsalicylate, carbamazepine, carbiphen, carprofen, carsalam, chlorobutanol, chlorthenoxazin, choline salicylate, cinchophen, cinmetacin, ciramadol, clidanac, clometacin, clonitazene, clonixin, clopirac, clove, codeine, codeine methyl bromide, codeine phosphate, codeine sulfate, cropropamide, crotethamide, desomorphine, dexoxadrol, dextromoramide, dezocine, diampromide, diclofenac sodium, difenamizole, difenpiramide, diflunisal, dihydrocodeine, dihydrocodeinone enol acetate, dihydromorphine, dihydroxyaluminum acetylsalicylate, dimenoxadol, dimepheptanol, dimethylthiambutene, dioxaphetyl butyrate, dipipanone, diprocetyl, dipyrone, ditazol, droxicam, emorfazone, enfenamic acid, epirizole, eptazocine, etersalate, ethenzamide, ethoheptazine, ethoxazene, ethylmethylthiambutene, ethylmorphine, etodolac, etofenamate, etonitazene, eugenol, felbinac, fenbufen, fenclozic acid, fendosal, fenoprofen, fentanyl, fentiazac, fepradinol, feprazone, floctafenine, flufenamic acid, flunoxaprofen, fluoresone, flupirtine, fluproquazone, flurbiprofen, fosfosal, gentisic acid, glafenine, glucametacin, glycol salicylate, guaiazulene, hydrocodone, hydromorphone, hydroxypethidine, ibufenac, ibuprofen, ibuproxam, imidazole salicylate, indomethacin, indoprofen, isofezolac, isoladol, isomethadone, isonixin, isoxepac, isoxicam, ketobemidone, ketoprofen, ketorolac, p-lactophenetide, lefetamine, levorphanol, lofentanil, lonazolac, lomoxicam, loxoprofen, lysine acetylsalicylate, magnesium acetylsalicylate, meclofenamic acid, mefenamic acid, meperidine, meptazinol, mesalamine, metazocine, methadone hydrochloride, methotrimeprazine, metiazinic acid, metofoline, metopon, mofebutazone, mofezolac, morazone, morphine, morphine hydrochloride, morphine sulfate, morpholine salicylate, myrophine, nabumetone, nalbuphine, 1-naphthyl salicylate, naproxen, narceine, nefopam, nicomorphine, nifenazone, niflumic acid, nimesulide, 5'-nitro-2'-propoxyacetanilide, norlevorphanol,

normethadone, normorphine, norpipanone, olsalazine, opium, oxaceprol, oxametacine, oxaprozin, oxycodone, oxymorphone, oxyphenbutazone, papaveretum, paranyline, parsalimide, pentazocine, perisoxal, phenacetin, phenadoxone, phenazocine, phenazopyridine hydrochloride, phenocoll, phenoperidine, phenopyrazone, phenyl acetylsalicylate, phenylbutazone, phenyl salicylate, phenyramidol, piketoprofen, piminodine, pipebuzone, piperylone, pirofen, pirazolac, piritramide, piroxicam, pranoprofen, proglumetacin, proheptazine, promedol, propacetamol, propiram, propoxyphene, propyphenazone, proquazone, protizinic acid, ramifenazone, remifentanil, rimazolium metilsulfate, salacetamide, salicin, salicylamide, salicylamide o-acetic acid, salicylsulfuric acid, salsalte, salverine, simetride, sodium salicylate, sufentanil, sulfasalazine, sulindac, superoxide dismutase, suprofen, suxibuzone, talniflumate, tenidap, tenoxicam, terofenamate, tetrandrine, thiazolinobutazone, tiaprofenic acid, tiaramide, tilidine, tinoridine, tolfenamic acid, tolmetin, tramadol, tropesin, viminol, xenbucin, ximoprofen, zaltoprofen, and zomepirac.

24. (Currently Amended) The ~~composition~~ pharmaceutical dosage form of any of claims 20, 21, 22, or 23, wherein the at least one ~~[[the]]~~ non-meloxicam active agent~~[[s]]~~ has an effective average particle size of less than ~~about~~ 2 microns.

25. (Currently Amended) The ~~composition~~ pharmaceutical dosage form of any of 20, 21, 22, or 23, wherein the at least one ~~[[the]]~~ non-meloxicam active agent~~[[s]]~~ is a conventional particle sized active agent.

26. (Withdrawn) A method of making a nanoparticulate composition comprising contacting meloxicam particles with at least one surface stabilizer for a time and under conditions sufficient to provide a nanoparticulate meloxicam composition having an effective average particle size of less than about 2000 nm, wherein the surface stabilizer is essentially free of intermolecular cross-linkages, and wherein in comparative pharmacokinetic testing with a non-nanoparticulate formulation of meloxicam having the same dosage strength and form, the

nanoparticulate composition exhibits a shorter time to T_{\max} when compared to the time to T_{\max} of the non-nanoparticulate meloxicam formulation.

27. (Withdrawn) The method of claim 26, wherein said contacting comprises grinding.

28. (Withdrawn) The method of claim 27, wherein said grinding comprises wet grinding.

29. (Withdrawn) The method of claim 26, wherein said contacting comprises homogenizing.

30. (Withdrawn) The method of claim 26, wherein said contacting comprises:
(a) dissolving the meloxicam particles in a solvent;
(b) adding the resulting meloxicam solution to a solution comprising at least one surface stabilizer; and
(c) precipitating the solubilized meloxicam having at least one surface stabilizer associated with the surface thereof by the addition thereto of a non-solvent.

31. (Withdrawn) The method of claim 26, wherein the meloxicam is selected from the group consisting of a crystalline phase, an amorphous phase, and a semi-crystalline phase.

32. (Withdrawn) The method of claim 26, wherein the effective average particle size of the nanoparticulate meloxicam particles is selected from the group consisting of less than about 1500 nm, less than about 1000 nm, less than about 900 nm, less than about 800 nm, less than about 700 nm, less than about 600 nm, less than about 500 nm, less than about 400 nm, less than about 300 nm, less than about 250 nm, less than about 200 nm, less than about 100 nm, less than about 75 nm, and less than about 50 nm.

33. (Withdrawn) The method of claim 26, wherein the composition is formulated for an administration form selected from the group consisting of oral, pulmonary, rectal, ophthalmic, colonic, parenteral, intracisternal, intravaginal, intraperitoneal, local, buccal, nasal, and topical administration.

34. (Withdrawn) The method of claim 26, wherein the composition is formulated into a dosage form selected from the group consisting of liquid dispersions, gels, aerosols, ointments, creams, controlled release formulations, fast melt formulations, lyophilized formulations, tablets, capsules, delayed release formulations, extended release formulations, pulsatile release formulations, and mixed immediate release and controlled release formulations.

35. (Withdrawn) The method of claim 26, wherein the composition further comprises one or more pharmaceutically acceptable excipients, carriers, or a combination thereof.

36. (Withdrawn) The method of claim 26, wherein the meloxicam is present in an amount selected from the group consisting of from about 99% to about 0.001%, from about 95% to about 0.5%, and from about 90% to about 0.5%, by weight, based on the total combined weight of the meloxicam and at least one surface stabilizer, not including other excipients.

37. (Withdrawn) The method of claim 26, wherein at least one surface stabilizer is present in an amount selected from the group consisting of from about 0.01% to about 99.5% by weight, from about 0.1% to about 95% by weight, and from about 0.5% to about 90% by weight, based on the total combined dry weight of the meloxicam and at least one surface stabilizer, not including other excipients.

38. (Withdrawn) The method of claim 26, comprising at least one primary surface stabilizer and at least one secondary surface stabilizer.

39. (Withdrawn) The method of claim 26, wherein the surface stabilizer is selected from the group consisting of an anionic surface stabilizer, a cationic surface stabilizer, and an ionic surface stabilizer.

40. (Withdrawn) The method of claim 39, wherein at least one surface stabilizer is selected from the group consisting of cetyl pyridinium chloride, gelatin, casein, phosphatides, dextran, glycerol, gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glycerol monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers, polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters, polyethylene glycols, dodecyl trimethyl ammonium bromide, polyoxyethylene stearates, colloidal silicon dioxide, phosphates, sodium dodecylsulfate, carboxymethylcellulose calcium, hydroxypropyl celluloses, hydroxypropyl methylcellulose, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hydroxypropylmethylcellulose phthalate, noncrystalline cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol, polyvinylpyrrolidone, 4-(1,1,3,3-tetramethylbutyl)-phenol polymer with ethylene oxide and formaldehyde, poloxamers; poloxamines, a charged phospholipid, dioctylsulfosuccinate, dialkylesters of sodium sulfosuccinic acid, sodium lauryl sulfate, alkyl aryl polyether sulfonates, mixtures of sucrose stearate and sucrose distearate, $C_{18}H_{37}CH_2C(O)N(CH_3)-CH_2(CHOH)_4(CH_2OH)_2$, p-isononylphenoxypoly-(glycidol), decanoyl-N-methylglucamide; n-decyl -D-glucopyranoside; n-decyl -D-maltopyranoside; n-dodecyl -D-glucopyranoside; n-dodecyl -D-maltoside; heptanoyl-N-methylglucamide; n-heptyl--D-glucopyranoside; n-heptyl -D-thioglucoside; n-hexyl -D-glucopyranoside; nonanoyl-N-methylglucamide; n-noyl -D-glucopyranoside; octanoyl-N-methylglucamide; n-octyl--D-glucopyranoside; octyl -D-thioglucopyranoside; lysozyme, PEG-phospholipid, PEG-cholesterol, PEG-cholesterol derivative, PEG-vitamin A, PEG-vitamin E, and random copolymers of vinyl acetate and vinyl pyrrolidone.

41. (Withdrawn) The method of claim 39, wherein at least one cationic surface stabilizer is selected from the group consisting of a polymer, a biopolymer, a polysaccharide, a cellulosic, an alginate, a nonpolymeric compound, and a phospholipid.

42. (Withdrawn) The method of claim 39, wherein the surface stabilizer is selected from the group consisting of cationic lipids, polymethylmethacrylate trimethylammonium bromide, sulfonium compounds, polyvinylpyrrolidone-2-dimethylaminoethyl methacrylate dimethyl sulfate, hexadecyltrimethyl ammonium bromide, phosphonium compounds, quaternary ammonium compounds, benzyl-di(2-chloroethyl)ethylammonium bromide, coconut trimethyl ammonium chloride, coconut trimethyl ammonium bromide, coconut methyl dihydroxyethyl ammonium chloride, coconut methyl dihydroxyethyl ammonium bromide, decyl triethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride bromide, C₁₂₋₁₅dimethyl hydroxyethyl ammonium chloride, C₁₂₋₁₅dimethyl hydroxyethyl ammonium chloride bromide, coconut dimethyl hydroxyethyl ammonium chloride, coconut dimethyl hydroxyethyl ammonium bromide, myristyl trimethyl ammonium methyl sulphate, lauryl dimethyl benzyl ammonium chloride, lauryl dimethyl benzyl ammonium bromide, lauryl dimethyl (ethenoxy)₄ ammonium chloride, lauryl dimethyl (ethenoxy)₄ ammonium bromide, N-alkyl (C₁₂₋₁₈)dimethylbenzyl ammonium chloride, N-alkyl (C₁₄₋₁₈)dimethyl-benzyl ammonium chloride, N-tetradecyldimethylbenzyl ammonium chloride monohydrate, dimethyl didecyl ammonium chloride, N-alkyl and (C₁₂₋₁₄) dimethyl 1-naphthylmethyl ammonium chloride, trimethylammonium halide, alkyl-trimethylammonium salts, dialkyl-dimethylammonium salts, lauryl trimethyl ammonium chloride, ethoxylated alkyamidoalkyldialkylammonium salt, an ethoxylated trialkyl ammonium salt, dialkylbenzene dialkylammonium chloride, N-didecyldimethyl ammonium chloride, N-tetradecyldimethylbenzyl ammonium, chloride monohydrate, N-alkyl(C₁₂₋₁₄) dimethyl 1-naphthylmethyl ammonium chloride, dodecyldimethylbenzyl ammonium chloride, dialkyl benzenealkyl ammonium chloride, lauryl trimethyl ammonium chloride, alkylbenzyl methyl ammonium chloride, alkyl benzyl

dimethyl ammonium bromide, C₁₂ trimethyl ammonium bromides, C₁₅ trimethyl ammonium bromides, C₁₇ trimethyl ammonium bromides, dodecylbenzyl triethyl ammonium chloride, polydiallyldimethylammonium chloride (DADMAC), dimethyl ammonium chlorides, alkyldimethylammonium halogenides, tricetyl methyl ammonium chloride, decyltrimethylammonium bromide, dodecyltriethylammonium bromide, tetradecyltrimethylammonium bromide, methyl trioctylammonium chloride, polyquaternium 10, tetrabutylammonium bromide, benzyl trimethylammonium bromide, choline esters, benzalkonium chloride, stearylalkonium chloride compounds, cetyl pyridinium bromide, cetyl pyridinium chloride, halide salts of quaternized polyoxyethylalkylamines, quaternized ammonium salt polymers, alkyl pyridinium salts; amines, amine salts, amine oxides, imide azolinium salts, protonated quaternary acrylamides, methylated quaternary polymers, and cationic guar.

43. (Withdrawn) The method of claim 26, wherein after preparation of a first nanoparticulate meloxicam composition, a second meloxicam composition having an effective average particle size of greater than about 2 microns is combined with the first nanoparticulate meloxicam composition.

44. (Withdrawn) The method of claim 26, wherein either prior to or subsequent to preparation of the nanoparticulate meloxicam composition, at least one non-meloxicam active agent is added to the meloxicam composition, wherein said non-meloxicam active agent is selected from the group consisting of proteins, peptides, nucleotides, anti-obesity drugs, nutraceuticals, dietary supplements, carotenoids, corticosteroids, elastase inhibitors, anti-fungals, alkylxanthine, oncology therapies, anti-emetics, analgesics, opioids, antipyretics, cardiovascular agents, anti-inflammatory agents, anthelmintics, anti-arrhythmic agents, antibiotics, anticoagulants, antidepressants, antidiabetic agents, antiepileptics, antihistamines, antihypertensive agents, antimuscarinic agents, antimycobacterial agents, antineoplastic agents, immunosuppressants, antithyroid agents, antiviral agents, anxiolytics, sedatives, astringents, beta-

adrenoceptor blocking agents, blood products, blood substitutes, cardiac inotropic agents, contrast media, corticosteroids, cough suppressants, diagnostic agents, diagnostic imaging agents, diuretics, dopaminergics, haemostatics, immunological agents, lipid regulating agents, muscle relaxants, parasympathomimetics, parathyroid calcitonin and biphosphonates, prostaglandins, radio- pharmaceuticals, sex hormones, anti-allergic agents, stimulants, anoretics, sympathomimetics, thyroid agents, Mu receptor antagonists, Kappa receptor antagonists, non-narcotic analgesics, monoamine uptake inhibitors, adenosine regulating agents, cannabinoid derivatives, Substance P antagonists, neurokinin-1 receptor antagonists, and sodium channel blockers.

45. (Withdrawn) The method of claim 44, wherein said nutraceutical is selected from the group consisting of lutein, folic acid, fatty acids, fruit extracts, vegetable extracts, vitamin supplements, mineral supplements, phosphatidylserine, lipoic acid, melatonin, glucosamine/chondroitin, Aloe Vera, Guggul, glutamine, amino acids, green tea, lycopene, whole foods, food additives, herbs, phytonutrients, antioxidants, flavonoid constituents of fruits, evening primrose oil, flax seeds, fish oils, marine animal oils, and probiotics.

46. (Withdrawn) The method of claim 44, wherein said anti-inflammatory agent is a COX-2 inhibitor selected from the group consisting of celecoxib, rofecoxib, valdecoxib, parecoxib, MK-966, etoricoxib, 4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)] benzenesulfonamide, N-(2-cyclohexyloxy-4-nitrophenyl)methane sulfonamide, methyl sulfone spiro(2.4)hept-5-ene I, SC-57666, celexcoxib, SC-558, SC-560, etodolac, 5,5-dimethyl-3-(3-fluorophenyl)-4-(4-methylsulfonyl)phenyl 2(5H)-furanone, MK-476, L-745337, L-761066, L-761000, L-748780, L-748731, 5-Bromo-2-(4-fluorophenyl)-3-(4-(methylsulfonyl)phenyl, 1-(7-tert.-butyl-2,3-dihydro-3,3-dimethylbenzo(b)furan-5-yl)-4-cyclopropylbutan-1-one, 3-formylamino-7-methylsulfonylamino-6-phenoxy-4H-1-benzopyran-4-one, BF 389, PD 136005, PD 142893, PD 145065, flurbiprofen, nimesulide, nabumetone, flosulide, piroxicam, dicofenac, COX-189, D 1367, 4 nitro 2 phenoxy methane sulfonanilide, (3 benzoyldifluoromethane

sulfonanilide, diflumidone), JTE-522, 4'-Acetyl-2'-(2,4-difluorophenoxy)methanesulfonanilide, FK 867, FR 115068, GR 253035, RWJ 63556, RWJ 20485, ZK 38997, (E)-(5)-(3,5-di-tert-butyl-4-hydroxybenzylidene)-2-ethyl-1,2-isothiazolidine-1,1-dioxide indomethacin, CL 1004, RS 57067, RS 104894, SC 41930, SB 205312, SKB 209670, and Ono 1078.

47. (Withdrawn) The method of claim 44, wherein said non-meloxicam active agent is selected from the group consisting of aceclofenac, acemetacin, e-acetamidocaproic acid, acetaminophen, acetaminosalol, acetanilide, acetylsalicylic acid, S-adenosylmethionine, alclofenac, alfentanil, allylprodine, alminoprofen, aloxiprin, alphaprodine, aluminum bis(acetylsalicylate), amfenac, aminochlorthenoxazin, 3-amino-4-hydroxybutyric acid, 2-amino-4-picoline, aminopropylon, aminopyrine, amixetrine, ammonium salicylate, ampiroxicam, amtolmetin guacil, anileridine, antipyrine, antipyrine salicylate, antrafenine, apazone, bendazac, benorylate, benoxaprofen, benzpiperylon, benzydamine, benzylmorphine, bermoprofen, bezitramide, -bisabolol, bromfenac, p-bromoacetanilide, 5-bromosalicylic acid acetate, bromosaligenin, buccetin, bucloxic acid, bucolome, bufexamac, bumadizon, buprenorphine, butacetin, butibufen, butophanol, calcium acetylsalicylate, carbamazepine, carbiphen, carprofen, carsalam, chlorobutanol, chlorthenoxazin, choline salicylate, cinchophen, cinmetacin, ciramadol, clidanac, clometacin, clonitazene, clonixin, clopirac, clove, codeine, codeine methyl bromide, codeine phosphate, codeine sulfate, cropropamide, crotethamide, desomorphine, dexoadrol, dextromoramide, dezocine, diampromide, diclofenac sodium, difenamizole, difenpiramide, diflunisal, dihydrocodeine, dihydrocodeinone enol acetate, dihydromorphine, dihydroxyaluminum acetylsalicylate, dimenoxadol, dimepheptanol, dimethylthiambutene, dioxaphetyl butyrate, dipipanone, diprocetyl, dipyrone, ditazol, droxicam, emorfazone, enfenamic acid, epirizole, eptazocine, etersalate, ethenzamide, ethoheptazine, ethoxazene, ethylmethylthiambutene, ethylmorphine, etodolac, etofenamate, etonitazene, eugenol, felbinac, fenbufen, fenclozic acid, fendosal, fenoprofen, fentanyl, fentiazac, fepradinol, feprazone, floctafenine, flufenamic acid, flunoxaprofen, fluoresone, flupirtine, fluproquazone, flurbiprofen, fosfosal, gentisic acid, glafenine, glucametacin, glycol salicylate, guaiazulene, hydrocodone,

hydromorphone, hydroxypethidine, ibufenac, ibuprofen, ibuproxam, imidazole salicylate, indomethacin, indoprofen, isofezolac, isoladol, isomethadone, isonixin, isoxepac, isoxicam, ketobemidone, ketoprofen, ketorolac, p-lactophenetide, lefetamine, levorphanol, lofentanil, lonazolac, lomoxicam, loxoprofen, lysine acetylsalicylate, magnesium acetylsalicylate, meclofenamic acid, mefenamic acid, meperidine, meptazinol, mesalamine, metazocine, methadone hydrochloride, methotrimeprazine, metiazinic acid, metofoline, metopon, mofebutazone, mofezolac, morazone, morphine, morphine hydrochloride, morphine sulfate, morpholine salicylate, myrophine, nabumetone, nalbuphine, 1-naphthyl salicylate, naproxen, narceine, nefopam, nicomorphine, nifenazone, niflumic acid, nimesulide, 5'-nitro-2'-propoxyacetanilide, norlevorphanol, normethadone, normorphine, norpipanone, olsalazine, opium, oxaceprol, oxametacine, oxaprozin, oxycodone, oxymorphone, oxyphenbutazone, papaveretum, paranyline, parsalmide, pentazocine, perisoxal, phenacetin, phenadoxone, phenazocine, phenazopyridine hydrochloride, phenocoll, phenoperidine, phenopyrazone, phenyl acetylsalicylate, phenylbutazone, phenyl salicylate, phenyramidol, piketoprofen, piminodine, pipebuzone, piperylone, pirofen, pirazolac, piritramide, piroxicam, pranoprofen, proglumetacin, proheptazine, promedol, propacetamol, propiram, propoxyphene, propyphenazone, proquazone, protizinic acid, ramifenazone, remifentanil, rimazolium metilsulfate, salacetamide, salicin, salicylamide, salicylamide o-acetic acid, salicylsulfuric acid, salsalte, salverine, simetride, sodium salicylate, sufentanil, sulfasalazine, sulindac, superoxide dismutase, suprofen, suxibuzone, talniflumate, tenidap, tenoxicam, terofenamate, tetrandrine, thiazolinobutazone, tiaprofenic acid, tiaramide, tilidine, tinoridine, tolfenamic acid, tolmetin, tramadol, tropesin, viminol, xenbucin, ximoprofen, zaltoprofen, and zomepirac.

48. (Withdrawn) The method of any of claims 44, 45, 46, or 47, wherein at least one non-meloxicam active agent has an effective average particle size of less than about 2 microns.

49. (Withdrawn) The method of any of claims 44, 45, 46, or 47, wherein at least one non-meloxicam active agent has an effective average particle size of greater than about 2 microns.

50. (Currently Amended) A method of treating a subject in need with a ~~nanoparticulate meloxicam formulation~~ comprising ~~administering~~ intravenously injecting to the subject an effective amount of a ~~nanoparticulate composition~~ pharmaceutical dosage form comprising:

- (a) a liquid dispersion medium;
- (b) meloxicam particles of meloxicam or a salt thereof; and
- (c) at least one polyvinylpyrrolidone, sodium deoxycholate, or a combination of polyvinylpyrrolidone and sodium deoxycholate as surface stabilizers,

wherein the surface stabilizer is essentially free of intermolecular cross-linkages, and wherein the meloxicam particles have an effective average particle size of less than ~~about~~ 2000 nm, ~~and wherein in comparative pharmacokinetic testing with a non-nanoparticulate formulation of meloxicam having the same dosage strength and form, the nanoparticulate composition exhibits a shorter time to T_{max} when compared to the time to T_{max} of the non-nanoparticulate meloxicam formulation.~~

51. (Previously Presented) The method of claim 50, wherein the meloxicam is selected from the group consisting of a crystalline phase, an amorphous phase, and a semi-crystalline phase.

52. (Currently Amended) The method of claim 50, wherein the effective average particle size of the nanoparticulate meloxicam particles is selected from the group consisting of less than ~~about~~ 1500 nm, less than ~~about~~ 1000 nm, less than ~~about~~ 900 nm, less than ~~about~~ 800 nm, less than ~~about~~ 700 nm, less than ~~about~~ 600 nm, less than ~~about~~ 500 nm, less than ~~about~~ 400 nm, less than ~~about~~ 300 nm, less than ~~about~~ 250 nm, less than ~~about~~ 200 nm, less than ~~about~~ 100 nm, less than ~~about~~ 75 nm, and less than ~~about~~ 50 nm.

53.-54. (Cancelled)

55. (Currently Amended) The method of claim 50, wherein the ~~composition~~ pharmaceutical dosage form further comprises one or more pharmaceutically acceptable excipients, carriers, or a combination thereof.

56. (Currently Amended) The method of claim 50, wherein the meloxicam is present in an amount selected from the group consisting of from ~~about~~ 99% to ~~about~~ 0.001%, from ~~about~~ 95% to ~~about~~ 0.5%, and from ~~about~~ 90% to ~~about~~ 0.5%, by weight, based on the total combined weight of the meloxicam and at least one surface stabilizer, not including other excipients.

57. (Currently Amended) The method of claim 50, wherein at least one surface stabilizer is present in an amount selected from the group consisting of from ~~about~~ 0.01% to ~~about~~ 99.5% by weight, from ~~about~~ 0.1% to ~~about~~ 95% by weight, and from ~~about~~ 0.5% to ~~about~~ 90% by weight, based on the total combined dry weight of meloxicam and at least one surface stabilizer, not including other excipients.

58.-63. (Cancelled)

64. (Currently Amended) The method of claim 50, wherein the C_{max} of the ~~nanoparticulate composition~~ pharmaceutical dosage form, when assayed in the plasma of the mammalian subject, is selected from the group consisting of greater than ~~about~~ 1 g/mL, greater than ~~about~~ 3 g/mL, greater than ~~about~~ 5 g/mL, greater than ~~about~~ 10 g/mL, and greater than ~~about~~ 15 g/mL.

65. (Previously Presented) The method of claim 50, wherein the method is used to treat a condition selected from the group consisting of conditions in which NSAIDs are contraindicated, arthritic disorders, gastrointestinal conditions, inflammatory conditions, pulmonary inflammation, ophthalmic diseases, central nervous systems disorders, pain, fever, inflammation-related cardiovascular disorders, angiogenesis-related disorders, benign tumors,

malignant tumors, adenomatous polyps, endometriosis, osteoporosis, dysmenorrhea, premature labor, asthma, fibrosis which occurs with radiation treatment, eosinophil-related disorders, pyrexia, bone resorption, nephrotoxicity, hypotension, arthrosis, joint stiffness, kidney disease, liver disease, acute mastitis, diarrhea, colonic adenomas, bronchitis, allergic neuritis, cytomegalovirus infectivity, apoptosis, lumbago, psoriasis, eczema, acne, burns, dermatitis, ultraviolet radiation damage, allergic rhinitis, respiratory distress syndrome, and endotoxin shock syndrome.

66. (Previously Presented) The method of claim 50, wherein the method is used to treat an indication in which anti-inflammatory agents, anti-angiogenesis agents, antitumorigenic agents, immunosuppressive agents, NSAIDs, COX-2 inhibitors, analgesic agents, anti-thrombotic agents, narcotics, or antifebrile agents are typically used.

67. (Previously Presented) The method of claim 50, wherein said subject is a human.

68. (Currently Amended) The method of claim 50, wherein said ~~composition~~ pharmaceutical dosage form additionally comprising at least one non-meloxicam active agent selected from the group consisting of proteins, peptides, nucleotides, anti-obesity drugs, nutraceuticals, dietary supplements, carotenoids, corticosteroids, elastase inhibitors, anti-fungals, alkylxanthine, oncology therapies, anti-emetics, analgesics, opioids, antipyretics, cardiovascular agents, anti-inflammatory agents, anthelmintics, anti-arrhythmic agents, antibiotics, anticoagulants, antidepressants, antidiabetic agents, antiepileptics, antihistamines, antihypertensive agents, antimuscarinic agents, antimycobacterial agents, antineoplastic agents, immunosuppressants, antithyroid agents, antiviral agents, anxiolytics, sedatives, astringents, beta-adrenoceptor blocking agents, blood products, blood substitutes, cardiac inotropic agents, contrast media, corticosteroids, cough suppressants, diagnostic agents, diagnostic imaging agents, diuretics, dopaminergics, haemostatics, immunological agents, lipid regulating agents, muscle relaxants, parasympathomimetics, parathyroid calcitonin and biphosphonates, prostaglandins, radio-pharmaceuticals, sex hormones, anti-allergic agents, stimulants, anoretics,

sympathomimetics, thyroid agents, Mu receptor antagonists, Kappa receptor antagonists, non-narcotic analgesics, monoamine uptake inhibitors, adenosine regulating agents, cannabinoid derivatives, Substance P antagonists, neurokinin-1 receptor antagonists, and sodium channel blockers.

69. (Previously Presented) The method of claim 68, wherein said nutraceutical is selected from the group consisting of lutein, folic acid, fatty acids, fruit extracts, vegetable extracts, vitamin supplements, mineral supplements, phosphatidylserine, lipoic acid, melatonin, glucosamine/chondroitin, Aloe Vera, Guggul, glutamine, amino acids, green tea, lycopene, whole foods, food additives, herbs, phytonutrients, antioxidants, flavonoid constituents of fruits, evening primrose oil, flax seeds, fish oils, marine animal oils, and probiotics.

70. (Previously Presented) The method of claim 68, wherein said anti-inflammatory agent is a COX-2 inhibitor selected from the group consisting of celecoxib, rofecoxib, valdecoxib, parecoxib, MK-966, etoricoxib, 4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide, N-(2-cyclohexyloxy-4-nitrophenyl)methane sulfonamide, methyl sulfone spiro(2.4)hept-5-ene I, SC-57666, celexcoxib, SC-558, SC-560, etodolac, 5,5-dimethyl-3-(3-fluorophenyl)-4-(4-methylsulfonyl)phenyl 2(5H)-furanone, MK-476, L-745337, L-761066, L-761000, L-748780, L-748731, 5-Bromo-2-(4-fluorophenyl)-3-(4-(methylsulfonyl)phenyl, 1-(7-tert.-butyl-2,3-dihydro-3,3-dimethylbenzo(b)furan-5-yl)-4-cyclopropylbutan-1-one, 3-formylamino-7-methylsulfonylamino-6-phenoxy-4H-1-benzopyran-4-one, BF 389, PD 136005, PD 142893, PD 145065, flurbiprofen, nimesulide, nabumetone, flosulide, piroxicam, dicofenac, COX-189, D 1367, 4 nitro 2 phenoxy methane sulfonanilide, (3 benzoyldifluoromethane sulfonanilide, diflumidone), JTE-522, 4'-Acetyl-2'-(2,4-difluorophenoxy)methanesulfonanilide, FK 867, FR 115068, GR 253035, RWJ 63556, RWJ 20485, ZK 38997, (E)-(5)-(3,5-di-tert-butyl-4-hydroxybenzylidene)-2-ethyl-1,2-isothiazolidine-1,1-dioxide indomethacin, CL 1004, RS 57067, RS 104894, SC 41930, SB 205312, SKB 209670, and Ono 1078.

71. (Previously Presented) The method of claim 68, wherein said non-meloxicam active agent is selected from the group consisting of aceclofenac, acemetacin, e-acetamidocaproic acid, acetaminophen, acetaminosalol, acetanilide, acetylsalicylic acid, S-adenosylmethionine, alclofenac, alfentanil, allylprodine, alminoprofen, aloxiprin, alphaprodine, aluminum bis(acetylsalicylate), amfenac, aminochlorthenoxazin, 3-amino-4-hydroxybutyric acid, 2-amino-4-picoline, aminopropylon, aminopyrine, amixetrine, ammonium salicylate, ampiroxicam, amtolmetin guacil, anileridine, antipyrine, antipyrine salicylate, antrafenine, apazone, bendazac, benorylate, benoxaprofen, benzpiperylon, benzydamine, benzylmorphine, bermoprofen, bezitramide, -bisabolol, bromfenac, p-bromoacetanilide, 5-bromosalicylic acid acetate, bromosaligenin, buccetin, bucloxic acid, bucolome, bufexamac, bumadizon, buprenorphine, butacetin, butibufen, butophanol, calcium acetylsalicylate, carbamazepine, carbiphen, carprofen, carsalam, chlorobutanol, chlorthenoxazin, choline salicylate, cinchophen, cinmetacin, ciramadol, clidanac, clometacin, clonitazene, clonixin, clopirac, clove, codeine, codeine methyl bromide, codeine phosphate, codeine sulfate, cropropamide, crotethamide, desomorphine, dexoadrol, dextromoramide, dezocine, diampromide, diclofenac sodium, difenamizole, difenpiramide, diflunisal, dihydrocodeine, dihydrocodeinone enol acetate, dihydromorphine, dihydroxyaluminum acetylsalicylate, dimenoxadol, dimepheptanol, dimethylthiambutene, dioxaphetyl butyrate, dipipanone, diprocetyl, dipyrone, ditazol, droxicam, emorfazone, enfenamic acid, epirizole, eptazocine, etersalate, ethenzamide, ethoheptazine, ethoxazene, ethylmethylthiambutene, ethylmorphine, etodolac, etofenamate, etonitazene, eugenol, felbinac, fenbufen, fenclozic acid, fendosal, fenoprofen, fentanyl, fentiazac, fepradinol, feprazone, floctafenine, flufenamic acid, flunoxaprofen, fluoresone, flupirtine, fluproquazone, flurbiprofen, fosfosal, gentisic acid, glafenine, glucametacin, glycol salicylate, guaiazulene, hydrocodone, hydromorphone, hydroxypethidine, ibufenac, ibuprofen, ibuproxam, imidazole salicylate, indomethacin, indoprofen, isofezolac, isoladol, isomethadone, isonixin, isoxepac, isoxicam, ketobemidone, ketoprofen, ketorolac, p-lactophenetide, lefetamine, levorphanol, lofentanil, lonazolac, lomoxicam, loxoprofen, lysine acetylsalicylate, magnesium acetylsalicylate,

meclofenamic acid, mefenamic acid, meperidine, meptazinol, mesalamine, metazocine, methadone hydrochloride, methotrimeprazine, metiazinic acid, metofoline, metopon, mofebutazone, mofezolac, morazone, morphine, morphine hydrochloride, morphine sulfate, morpholine salicylate, myrophine, nabumetone, nalbuphine, 1-naphthyl salicylate, naproxen, narceine, nefopam, nicomorphine, nifenazone, niflumic acid, nimesulide, 5'-nitro-2'-propoxyacetanilide, norlevorphanol, normethadone, normorphine, norpipanone, olsalazine, opium, oxaceprol, oxametacine, oxaprozin, oxycodone, oxymorphone, oxyphenbutazone, papaveretum, paranyline, parsalimide, pentazocine, perisoxal, phenacetin, phenadoxone, phenazocine, phenazopyridine hydrochloride, phenocoll, phenoperidine, phenopyrazone, phenyl acetylsalicylate, phenylbutazone, phenyl salicylate, phenylamidol, piketoprofen, piminodine, pipebuzone, piperylone, pirofen, pirazolac, piritramide, piroxicam, pranoprofen, proglumetacin, proheptazine, promedol, propacetamol, propiram, propoxyphene, propyphenazone, proquazone, protizinic acid, ramifenazone, remifentanil, rimazolium metilsulfate, salacetamide, salicin, salicylamide, salicylamide o-acetic acid, salicylsulfuric acid, salsalte, salverine, simetride, sodium salicylate, sufentanil, sulfasalazine, sulindac, superoxide dismutase, suprofen, suxibuzone, talniflumate, tenidap, tenoxicam, terofenamate, tetrandrine, thiazolinobutazone, tiaprofenic acid, tiaramide, tilidine, tinoridine, tolfenamic acid, tolmetin, tramadol, tropesin, viminol, xenbucin, ximoprofen, zaltoprofen, and zomepirac.

72. (Currently Amended) The method of any of claims 68, 69, 70, or 71, wherein at least one non-meloxicam active agent has an effective average particle size of less than ~~about~~ 2 microns.

73. (Cancelled)

74. (New) A pharmaceutical dosage form suitable for intravenous injection comprising:

(a) a liquid dispersion medium;

(b) particles of meloxicam or a salt thereof having an effective average particle size of less than 2000 nm;

(b) at least one surface stabilizer adsorbed on the surface of the meloxicam particles selected from the group consisting of an anionic surface stabilizer, a cationic surface stabilizer, and an ionic surface stabilizer, wherein the surface stabilizer is essentially free of intermolecular cross-linkages.

75. (New) The pharmaceutical dosage form of claim 74, wherein the meloxicam is selected from the group consisting of a crystalline phase, an amorphous phase, and a semi-crystalline phase.

76. (New) The pharmaceutical dosage form of claim 74, wherein the effective average particle size of the nanoparticulate meloxicam particles is selected from the group consisting of less than 1500 nm, less than 1000 nm, less than 900 nm, less than 800 nm, less than 700 nm, less than 600 nm, less than 500 nm, less than 400 nm, less than 300 nm, less than 250 nm, less than 200 nm, less than 100 nm, less than 75 nm, and less than 50 nm.

77. (New) The pharmaceutical dosage form of claim 74, wherein the pharmaceutical dosage form further comprises one or more pharmaceutically acceptable excipients, carriers, or a combination thereof.

78. (New) The pharmaceutical dosage form of claim 74, wherein the meloxicam is present in an amount selected from the group consisting of from 99.5% to 0.001%, from 95% to 0.1%, and from 90% to 0.5%, by weight, based on the total combined weight of the meloxicam and at least one surface stabilizer, not including other excipients.

79. (New) The pharmaceutical dosage form of claim 74, wherein the at least one surface stabilizer is present in an amount selected from the group consisting of from 0.01% to 99.5% by weight, from 0.1% to 95% by weight, and from 0.5% to 90% by weight, based on the

total combined dry weight of meloxicam and at least one surface stabilizer, not including other excipients.

80. (New) The pharmaceutical dosage form of claim 74, wherein the at least one surface stabilizer is selected from the group consisting of cetyl pyridinium chloride, gelatin, casein, phosphatides, dextran, glycerol, gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glycerol monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, sodium deoxycholate, polyoxyethylene alkyl ethers, polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters, polyethylene glycols, dodecyl trimethyl ammonium bromide, polyoxyethylene stearates, colloidal silicon dioxide, phosphates, sodium dodecylsulfate, carboxymethylcellulose calcium, hydroxypropyl celluloses, hydroxypropyl methylcellulose, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hydroxypropylmethyl-cellulose phthalate, noncrystalline cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol, polyvinylpyrrolidone, 4-(1,1,3,3-tetramethylbutyl)-phenol polymer with ethylene oxide and formaldehyde, poloxamers; poloxamines, a charged phospholipid, dioctylsulfosuccinate, dialkylesters of sodium sulfosuccinic acid, sodium lauryl sulfate, alkyl aryl polyether sulfonates, mixtures of sucrose stearate and sucrose distearate, $C_{18}H_{37}CH_2C(O)N(CH_3)-CH_2(CHOH)_4(CH_2OH)_2$, p-isononylphenoxypoly-(glycidol), decanoyl-N-methylglucamide; n-decyl -D-glucopyranoside; n-decyl -D-maltopyranoside; n-dodecyl -D-glucopyranoside; n-dodecyl -D-maltoside; heptanoyl-N-methylglucamide; n-heptyl--D-glucopyranoside; n-heptyl -D-thioglucoside; n-hexyl -D-glucopyranoside; nonanoyl-N-methylglucamide; n-nonyl -D-glucopyranoside; octanoyl-N-methylglucamide; n-octyl--D-glucopyranoside; octyl -D-thioglucopyranoside; lysozyme, PEG-phospholipid, PEG-cholesterol, PEG-cholesterol derivative, PEG-vitamin A, PEG-vitamin E, and random copolymers of vinyl acetate and vinyl pyrrolidone.

81. (New) The pharmaceutical dosage form of claim 74, wherein at least one cationic surface stabilizer is selected from the group consisting of a polymer, a biopolymer, a polysaccharide, a cellulosic, an alginate, a nonpolymeric compound, and a phospholipid.

82. (New) The pharmaceutical dosage form of claim 74, wherein the surface stabilizer is selected from the group consisting of cationic lipids, polymethylmethacrylate trimethylammonium bromide, sulfonium compounds, polyvinylpyrrolidone-2-dimethylaminoethyl methacrylate dimethyl sulfate, hexadecyltrimethyl ammonium bromide, phosphonium compounds, quarternary ammonium compounds, benzyl-di(2-chloroethyl)ethylammonium bromide, coconut trimethyl ammonium chloride, coconut trimethyl ammonium bromide, coconut methyl dihydroxyethyl ammonium chloride, coconut methyl dihydroxyethyl ammonium bromide, decyl triethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride bromide, C₁₂₋₁₅dimethyl hydroxyethyl ammonium chloride, C₁₂₋₁₅dimethyl hydroxyethyl ammonium chloride bromide, coconut dimethyl hydroxyethyl ammonium chloride, coconut dimethyl hydroxyethyl ammonium bromide, myristyl trimethyl ammonium methyl sulphate, lauryl dimethyl benzyl ammonium chloride, lauryl dimethyl benzyl ammonium bromide, lauryl dimethyl (ethenoxy)₄ ammonium chloride, lauryl dimethyl (ethenoxy)₄ ammonium bromide, N-alkyl (C₁₂₋₁₈)dimethylbenzyl ammonium chloride, N-alkyl (C₁₄₋₁₈)dimethyl-benzyl ammonium chloride, N-tetradecyldimethylbenzyl ammonium chloride monohydrate, dimethyl didecyl ammonium chloride, N-alkyl and (C₁₂₋₁₄) dimethyl 1-naphthylmethyl ammonium chloride, trimethylammonium halide, alkyl-trimethylammonium salts, dialkyl-dimethylammonium salts, lauryl trimethyl ammonium chloride, ethoxylated alkyamidoalkyldialkylammonium salt, an ethoxylated trialkyl ammonium salt, dialkylbenzene dialkylammonium chloride, N-didecyldimethyl ammonium chloride, N-tetradecyldimethylbenzyl ammonium, chloride monohydrate, N-alkyl(C₁₂₋₁₄) dimethyl 1-naphthylmethyl ammonium chloride, dodecyldimethylbenzyl ammonium chloride, dialkyl benzenealkyl ammonium chloride, lauryl

trimethyl ammonium chloride, alkylbenzyl methyl ammonium chloride, alkyl benzyl dimethyl ammonium bromide, C₁₂ trimethyl ammonium bromides, C₁₅ trimethyl ammonium bromides, C₁₇ trimethyl ammonium bromides, dodecylbenzyl triethyl ammonium chloride, polydiallyldimethylammonium chloride (DADMAC), dimethyl ammonium chlorides, alkyldimethylammonium halogenides, tricetyl methyl ammonium chloride, decyltrimethylammonium bromide, dodecyltriethylammonium bromide, tetradecyltrimethylammonium bromide, methyl trioctylammonium chloride, polyquaternium 10, tetrabutylammonium bromide, benzyl trimethylammonium bromide, choline esters, benzalkonium chloride, stearalkonium chloride compounds, cetyl pyridinium bromide, cetyl pyridinium chloride, halide salts of quaternized polyoxyethylalkylamines, quaternized ammonium salt polymers, alkyl pyridinium salts; amines, amine salts, amine oxides, imide azolinium salts, protonated quaternary acrylamides, methylated quaternary polymers, and cationic guar.

83. (New) The pharmaceutical dosage form of claim 74, wherein the C_{max} of the pharmaceutical dosage form, when assayed in the plasma of the mammalian subject, is selected from the group consisting of greater than 1 g/mL, greater than 3 g/mL, greater than 5 g/mL, greater than 10 g/mL, and greater than 15 g/mL.

84. (New) The pharmaceutical dosage form of claim 74, additionally comprising a meloxicam composition having an effective average particle size which is greater than 2 microns.

85. (New) The pharmaceutical dosage form of claim 74, additionally comprising at least one additional nanoparticulate meloxicam composition, having an effective average particle size of less than 2 microns, wherein said additional nanoparticulate meloxicam composition has an effective average particle size which is different than particle size of the pharmaceutical dosage form of claim 74.

86. (New) The pharmaceutical dosage form of claim 74, additionally comprising at least one non-meloxicam active agent selected from the group consisting of proteins, peptides, nucleotides, anti-obesity drugs, nutraceuticals, dietary supplements, carotenoids, corticosteroids, elastase inhibitors, anti-fungals, alkylxanthine, oncology therapies, anti-emetics, analgesics, opioids, antipyretics, cardiovascular agents, anti-inflammatory agents, anthelmintics, anti-arrhythmic agents, antibiotics, anticoagulants, antidepressants, antidiabetic agents, antiepileptics, antihistamines, antihypertensive agents, antimuscarinic agents, antimycobacterial agents, antineoplastic agents, immunosuppressants, antithyroid agents, antiviral agents, anxiolytics, sedatives, astringents, beta-adrenoceptor blocking agents, blood products, blood substitutes, cardiac inotropic agents, contrast media, corticosteroids, cough suppressants, diagnostic agents, diagnostic imaging agents, diuretics, dopaminergics, haemostatics, immunological agents, lipid regulating agents, muscle relaxants, parasympathomimetics, parathyroid calcitonin and biphosphonates, prostaglandins, radio- pharmaceuticals, sex hormones, anti-allergic agents, stimulants, anoretics, sympathomimetics, thyroid agents, Mu receptor antagonists, Kappa receptor antagonists, non-narcotic analgesics, monoamine uptake inhibitors, adenosine regulating agents, cannabinoid derivatives, Substance P antagonists, neurokinin-1 receptor antagonists, and sodium channel blockers.

87. (New) A pharmaceutical dosage form suitable for intravenous injection comprising:

- (a) a liquid dispersion medium;
- (b) particles of meloxicam or a salt thereof having an effective average particle size of less than 2000 nm;
- (b) at least one surface stabilizer adsorbed on the surface of the meloxicam particles, wherein the surface stabilizer is essentially free of intermolecular cross-linkages.

88. (New) The pharmaceutical dosage form of claim 74, wherein the meloxicam is selected from the group consisting of a crystalline phase, an amorphous phase, and a semi-crystalline phase.

89. (New) The pharmaceutical dosage form of claim 87, wherein the surface stabilizer is selected from the group consisting of an anionic surface stabilizer, a cationic surface stabilizer, and an ionic surface stabilizer

90. (New) The pharmaceutical dosage form of claim 87, wherein the effective average particle size of the nanoparticulate meloxicam particles is selected from the group consisting of less than 1500 nm, less than 1000 nm, less than 900 nm, less than 800 nm, less than 700 nm, less than 600 nm, less than 500 nm, less than 400 nm, less than 300 nm, less than 250 nm, less than 200 nm, less than 100 nm, less than 75 nm, and less than 50 nm.

91. (New) The pharmaceutical dosage form of claim 87, wherein the pharmaceutical dosage form further comprises one or more pharmaceutically acceptable excipients, carriers, or a combination thereof.

92. (New) The pharmaceutical dosage form of claim 87, wherein the meloxicam is present in an amount selected from the group consisting of from 99.5% to 0.001%, from 95% to 0.1%, and from 90% to 0.5%, by weight, based on the total combined weight of the meloxicam and at least one surface stabilizer, not including other excipients.

93. (New) The pharmaceutical dosage form of claim 87, wherein the at least one surface stabilizer is present in an amount selected from the group consisting of from 0.01% to 99.5% by weight, from 0.1% to 95% by weight, and from 0.5% to 90% by weight, based on the total combined dry weight of meloxicam and at least one surface stabilizer, not including other excipients.

94. (New) The pharmaceutical dosage form of claim 87, wherein the at least one surface stabilizer is selected from the group consisting of cetyl pyridinium chloride, gelatin, casein, phosphatides, dextran, glycerol, gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glycerol monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, sodium deoxycholate, polyoxyethylene alkyl ethers, polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters, polyethylene glycols, dodecyl trimethyl ammonium bromide, polyoxyethylene stearates, colloidal silicon dioxide, phosphates, sodium dodecylsulfate, carboxymethylcellulose calcium, hydroxypropyl celluloses, hydroxypropyl methylcellulose, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hydroxypropylmethyl-cellulose phthalate, noncrystalline cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol, polyvinylpyrrolidone, 4-(1,1,3,3-tetramethylbutyl)-phenol polymer with ethylene oxide and formaldehyde, poloxamers; poloxamines, a charged phospholipid, dioctylsulfosuccinate, dialkylesters of sodium sulfosuccinic acid, sodium lauryl sulfate, alkyl aryl polyether sulfonates, mixtures of sucrose stearate and sucrose distearate, $C_{18}H_{37}CH_2C(O)N(CH_3)-CH_2(CHOH)_4(CH_2OH)_2$, p-isononylphenoxy-poly-(glycidol), decanoyl-N-methylglucamide; n-decyl -D-glucopyranoside; n-decyl -D-maltopyranoside; n-dodecyl -D-glucopyranoside; n-dodecyl -D-maltoside; heptanoyl-N-methylglucamide; n-heptyl--D-glucopyranoside; n-heptyl -D-thioglucoside; n-hexyl -D-glucopyranoside; nonanoyl-N-methylglucamide; n-nonyl -D-glucopyranoside; octanoyl-N-methylglucamide; n-octyl--D-glucopyranoside; octyl -D-thioglucopyranoside; lysozyme, PEG-phospholipid, PEG-cholesterol, PEG-cholesterol derivative, PEG-vitamin A, PEG-vitamin E, and random copolymers of vinyl acetate and vinyl pyrrolidone.

95. (New) The pharmaceutical dosage form of claim 87, wherein at least one cationic surface stabilizer is selected from the group consisting of a polymer, a biopolymer, a polysaccharide, a cellulosic, an alginate, a nonpolymeric compound, and a phospholipid.

96. (New) The pharmaceutical dosage form of claim 87, wherein the surface stabilizer is selected from the group consisting of cationic lipids, polymethylmethacrylate trimethylammonium bromide, sulfonium compounds, polyvinylpyrrolidone-2-dimethylaminoethyl methacrylate dimethyl sulfate, hexadecyltrimethyl ammonium bromide, phosphonium compounds, quarternary ammonium compounds, benzyl-di(2-chloroethyl)ethylammonium bromide, coconut trimethyl ammonium chloride, coconut trimethyl ammonium bromide, coconut methyl dihydroxyethyl ammonium chloride, coconut methyl dihydroxyethyl ammonium bromide, decyl triethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride bromide, C₁₂₋₁₅ dimethyl hydroxyethyl ammonium chloride, C₁₂₋₁₅ dimethyl hydroxyethyl ammonium chloride bromide, coconut dimethyl hydroxyethyl ammonium chloride, coconut dimethyl hydroxyethyl ammonium bromide, myristyl trimethyl ammonium methyl sulphate, lauryl dimethyl benzyl ammonium chloride, lauryl dimethyl benzyl ammonium bromide, lauryl dimethyl (ethenoxy)₄ ammonium chloride, lauryl dimethyl (ethenoxy)₄ ammonium bromide, N-alkyl (C₁₂₋₁₈) dimethylbenzyl ammonium chloride, N-alkyl (C₁₄₋₁₈) dimethyl-benzyl ammonium chloride, N-tetradecylidmethylbenzyl ammonium chloride monohydrate, dimethyl didecyl ammonium chloride, N-alkyl and (C₁₂₋₁₄) dimethyl 1-naphthylmethyl ammonium chloride, trimethylammonium halide, alkyl-trimethylammonium salts, dialkyl-dimethylammonium salts, lauryl trimethyl ammonium chloride, ethoxylated alkyamidoalkyldialkylammonium salt, an ethoxylated trialkyl ammonium salt, dialkylbenzene dialkylammonium chloride, N-didecyldimethyl ammonium chloride, N-tetradecyldimethylbenzyl ammonium, chloride monohydrate, N-alkyl(C₁₂₋₁₄) dimethyl 1-naphthylmethyl ammonium chloride, dodecyldimethylbenzyl ammonium chloride, dialkyl benzenealkyl ammonium chloride, lauryl trimethyl ammonium chloride, alkylbenzyl methyl ammonium chloride, alkyl benzyl dimethyl ammonium bromide, C₁₂ trimethyl ammonium bromides, C₁₅ trimethyl ammonium bromides, C₁₇ trimethyl ammonium bromides, dodecylbenzyl triethyl ammonium chloride, poly-

diallyldimethylammonium chloride (DADMAC), dimethyl ammonium chlorides, alkyl dimethylammonium halogenides, tricetyl methyl ammonium chloride, decyltrimethylammonium bromide, dodecyltriethylammonium bromide, tetradecyltrimethylammonium bromide, methyl trioctylammonium chloride, polyquaternium 10, tetrabutylammonium bromide, benzyl trimethylammonium bromide, choline esters, benzalkonium chloride, stearylalkonium chloride compounds, cetyl pyridinium bromide, cetyl pyridinium chloride, halide salts of quaternized polyoxyethylalkylamines, quaternized ammonium salt polymers, alkyl pyridinium salts; amines, amine salts, amine oxides, imide azolinium salts, protonated quaternary acrylamides, methylated quaternary polymers, and cationic guar.

97. (New) The pharmaceutical dosage form of claim 87, wherein the C_{\max} of the pharmaceutical dosage form, when assayed in the plasma of the mammalian subject, is selected from the group consisting of greater than 1 g/mL, greater than 3 g/mL, greater than 5 g/mL, greater than 10 g/mL, and greater than 15 g/mL.

98. (New) The pharmaceutical dosage form of claim 87, additionally comprising a meloxicam composition having an effective average particle size which is greater than 2 microns.

99. (New) The pharmaceutical dosage form of claim 87, additionally comprising at least one additional nanoparticulate meloxicam composition, having an effective average particle size of less than 2 microns, wherein said additional nanoparticulate meloxicam composition has an effective average particle size which is different than particle size of the pharmaceutical dosage form of claim 74.

100. (New) The pharmaceutical dosage form of claim 87, additionally comprising at least one non-meloxicam active agent selected from the group consisting of proteins, peptides, nucleotides, anti-obesity drugs, nutraceuticals, dietary supplements, carotenoids, corticosteroids, elastase inhibitors, anti-fungals, alkylxanthine, oncology therapies, anti-emetics, analgesics,

opioids, antipyretics, cardiovascular agents, anti-inflammatory agents, anthelmintics, anti-arrhythmic agents, antibiotics, anticoagulants, antidepressants, antidiabetic agents, antiepileptics, antihistamines, antihypertensive agents, antimuscarinic agents, antimycobacterial agents, antineoplastic agents, immunosuppressants, antithyroid agents, antiviral agents, anxiolytics, sedatives, astringents, beta-adrenoceptor blocking agents, blood products, blood substitutes, cardiac inotropic agents, contrast media, corticosteroids, cough suppressants, diagnostic agents, diagnostic imaging agents, diuretics, dopaminergics, haemostatics, immunological agents, lipid regulating agents, muscle relaxants, parasympathomimetics, parathyroid calcitonin and biphosphonates, prostaglandins, radio- pharmaceuticals, sex hormones, anti-allergic agents, stimulants, anoretics, sympathomimetics, thyroid agents, Mu receptor antagonists, Kappa receptor antagonists, non-narcotic analgesics, monoamine uptake inhibitors, adenosine regulating agents, cannabinoid derivatives, Substance P antagonists, neurokinin-1 receptor antagonists, and sodium channel blockers.

In re Marek Z. KUBIN and
Raymond G. Goodwin.

No. 2008-1184.

United States Court of Appeals,
Federal Circuit.

April 3, 2009.

Background: Applicants for patents related to claimed biotechnology invention for isolating and sequencing of human gene that encoded particular domain of protein, specifically DNA molecules, or polynucleotides, encoding polypeptide known as Natural Killer Cell Activation Inducing Ligand (NAIL). The United States Patent and Trademark Office, Board of Patent Appeals and Interferences, 2007 WL 2070495, rejected claims as obvious and invalid for lack of written description. Applicants appealed.

Holding: The Court of Appeals, Rader, Circuit Judge, held that claimed gene sequence was unpatentably obvious in light of abundant prior art.

Affirmed.

1. Patents \S 113(6)

Court of Appeals reviews factual findings by the Board of Patent Appeals and Interferences for lack of substantial evidence, and the Board's legal conclusions without deference.

2. Patents \S 16.13

In determining patentability, obviousness of a claimed invention is a question of law based on underlying findings of fact. 35 U.S.C.A. \S 103.

3. Patents \S 16(2, 3), 36.1(1)

An analysis of obviousness to determine patentability must be based on several factual inquiries: (1) the scope and content of the prior art, (2) the differences between the prior art and the claims at issue, (3) the level of ordinary skill in the art at the time the invention was made,

and (4) objective evidence of nonobviousness, if any. 35 U.S.C.A. \S 103.

4. Patents \S 16.13

The teachings of a prior art reference are underlying factual questions in the obviousness inquiry for patentability of a claimed invention. 35 U.S.C.A. \S 103.

5. Patents \S 36(3)

Board of Patent Appeals and Interferences' conclusion, in rejecting claims of patent application for isolating human gene sequence for natural killer cell activation inducing ligand (NAIL), that claimed sequence was obvious in light of abundant prior art, was supported by substantial evidence including that application disclosed use of standard biochemical methods outlined in prior art to isolate gene sequence for NAIL, that researcher of ordinary skill in art would have recognized that prior art discussed detailed protocol for identifying, isolating, and cloning equivalent of NAIL, that prior art did not teach away from combining its teachings with other references regarding gene sequence, and that skilled artisan would have had resoundingly reasonable expectation of success in deriving claimed invention in light of teachings of prior art. 35 U.S.C.A. \S 103(a).

6. Patents \S 16.5(1)

A prior art reference may be said to "teach away" when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the patent applicant. 35 U.S.C.A. \S 103.

See publication Words and Phrases for other judicial constructions and definitions.

Patents \S 328(2)

5,688,690. Cited as Prior Art.

Barbara R. Rudolph, Finnegan, Henderson, Farabow, Garrett & Dunner, L.L.P., of Washington, DC, argued for appellants. With her on the brief were Herbert H. Mintz and Bart A. Gerstenblith. Of counsel was Stuart L. Watt, Wendy A. Whiteford and Gail A. Katz, Amgen Inc., of Thousand Oaks, CA, and Kathleen Fowler, of Seattle, WA.

Janet A. Gongola, Associate Solicitor, Office of the Solicitor, United States Patent and Trademark Office, of Arlington, VA, argued for the Director of the United States Patent and Trademark Office. With her on the brief were William G. Jenks, Mary L. Kelly, and Stephen Walsh, Associate Solicitors. Of counsel was Raymond T. Chen, Associate Solicitor.

Rouget F. Henschel, Foley & Lardner LLP, of Washington, DC, for amicus curiae Biotechnology Industry Organization. With him on the brief were Stephen B. Maebius and Philip G. Kiko. Of counsel was Hans Sauer, Biotechnology Industry Organization, of Washington, DC, and Brian P. Barrett, Eli Lilly and Company, of Indianapolis, IN.

Matthew I. Kreeger, Morrison & Foerster LLP, of San Francisco, CA, for amicus curiae Novartis Vaccines and Diagnostics, Inc. Of counsel on the brief was Beth S. Brinkmann, of Washington, DC.

Jeffrey P. Kushan, Sidley Austin LLP, of Washington, DC, for amici curiae GlaxoSmithKline, et al. With him on the brief were Paul J. Zegger, Jon P. Santamauro, and Eric M. Solovy.

James J. Kelley, Eli Lilly and Company, of Indianapolis, IN, for amicus curiae Eli Lilly and Company. With him on the brief were MaryAnn Wiskerchen, Gregory A. Cox, Steven P. Caltrider and Robert A. Armitage.

Before RADER, FRIEDMAN, and LINN, Circuit Judges.

RADER, Circuit Judge.

Marek Kubin and Raymond Goodwin ("appellants") appeal from a decision of the Board of Patent Appeals and Interferences (the "Board") rejecting the claims of U.S. Patent Application Serial No. 09/667,859 ("859 Application") as obvious under 35 U.S.C. § 103(a) and invalid under 35 U.S.C. § 112 ¶ 1 for lack of written description. *Ex parte Kubin*, No. 2007-0819, 83 U.S.P.Q.2d 1410 (B.P.A.I.2007) ("Board Decision"). Because the Board correctly determined that appellants' claims are unpatentably obvious, this court affirms.

I.

This case presents a claim to a classic biotechnology invention—the isolation and sequencing of a human gene that encodes a particular domain of a protein. This court provided a primer on the basics of this technology in *In re O'Farrell*, 853 F.2d 894, 895-99 (Fed.Cir.1988). Specifically, appellants claim DNA molecules ("polynucleotides") encoding a protein ("polypeptide") known as the Natural Killer Cell Activation Inducing Ligand ("NAIL").

Natural Killer ("NK") cells, thought to originate in the bone marrow, are a class of cytotoxic lymphocytes that play a major role in fighting tumors and viruses. NK cells express a number of surface molecules which, when stimulated, can activate cytotoxic mechanisms. NAIL is a specific receptor protein on the cell surface that plays a role in activating the NK cells.

The specification of the claimed invention recites an amino acid sequence of a NAIL polypeptide. The invention further isolates and sequences a polynucleotide that encodes a NAIL polypeptide. Moreover, the inventors trumpet their alleged discovery of a binding relationship between NAIL and a protein known as CD48. The NAIL-CD48 interaction has

important biological consequences for NK cells, including an increase in cell cytotoxicity and in production of interferon. Representative claim 73 of appellants' application claims the DNA that encodes the CD48-binding region of NAIL proteins:

73. An isolated nucleic acid molecule comprising a polynucleotide encoding a polypeptide at least 80% identical to amino acids 22-221 of SEQ ID NO:2, wherein the polypeptide binds CD48.

In other words, appellants claim a genus of isolated polynucleotides encoding a protein that binds CD48 and is at least 80% identical to amino acids 22-221 of SEQ ID NO:2—the disclosed amino acid sequence for the CD48-binding region of NAIL.

Appellants' specification discloses nucleotide sequences for two polynucleotides falling within the scope of the claimed genus, namely SEQ ID NO:1 and SEQ ID NO:3. SEQ ID NO: 1 recites the specific coding sequence of NAIL, whereas SEQ ID NO: 3 recites the full NAIL gene, including upstream and downstream non-coding sequences. The specification also contemplates variants of NAIL that retain the same binding properties:

Variants include polypeptides that are substantially homologous to the native form, but which have an amino acid sequence different from that of the native form because of one or more deletions, insertions or substitutions. Particular embodiments include, but are not limited to, polypeptides that comprise from one to ten deletions, insertions or substitutions of amino acid residues, when compared to a native sequence.

A given amino acid may be replaced, for example, by a residue having similar physiochemical characteristics. Examples of such conservative substitutions include substitution of one aliphatic residue for another, such as Ile, Val, Leu, or Ala for one another; substitutions of one polar residue for another, such as be-

tween Lys and Arg, Glu and Asp, or Gln and Asn; or substitutions of one aromatic residue for another, such as Phe, Trp, or Tyr for one another. Other conservative substitutions, e.g., involving substitutions of entire regions having similar hydrophobicity characteristics, are well known.

'859 Application at 26. However, the specification does not indicate any example variants of NAIL that make these conservative amino acid substitutions.

II.

The Board rejected appellants' claims as invalid under both § 103 and § 112. With regard to the § 112 rejection, the Board found the genus of nucleic acids of representative claim 73 unsupported by an adequate written description. First, the Board observed that although appellants had sequenced two nucleic acids falling within the scope of claim 73, they had not disclosed any variant species where amino acids 22-221 were different in any way from the disclosed SEQ ID NO:2 sequence. Thus, the Board concluded that appellants were not entitled to their genus claim of DNA molecules encoding proteins 80% identical to SEQ ID NO:2:

[Appellants] have not described what domains of those sequences are correlated with the required binding to CD48, and thus have not described which of NAIL's amino acids can be varied and still maintain binding. Thus . . . their Specification would not have shown possession of a sufficient number of sequences falling within their potentially large genus to establish possession of their claimed genus.

Without a correlation between structure and function, the claim does little more than define the claimed invention by

function. That is not sufficient to satisfy the written description requirement.

Board Decision at 16–17.

Regarding obviousness, the Board rejected appellants' claims over the combined teachings of U.S. Patent No. 5,688,690 ("Valiante") and 2 Joseph Sambrook et al., *Molecular Cloning: A Laboratory Manual* 43–84 (2d ed.1989) ("Sambrook"). The Board also considered, but found to be cumulative to Valiante and Sambrook, Porunelloor Mathew et al., *Cloning and Characterization of the 2B4 Gene Encoding a Molecule Associated with Non-MHC-Restricted Killing Mediated by Activated Natural Killer Cells and T Cells*, 151 J. Immunology 5328–37 (1993) ("Mathew").

Valiante discloses a receptor protein called "p38" that is found on the surface of human NK cells. Valiante teaches that the p38 receptor is present on virtually all human NK cells and "can serve as an activation marker for cytotoxic NK cells." '690 Patent col.3 ll.3–4; *see also id.* at col.5 ll.6–7 ("Stimulation of p38 results in activation of cytotoxicity"). Valiante also discloses and claims a monoclonal antibody specific for p38 called "mAb C1.7." The Board found (and appellants do not dispute) that Valiante's p38 protein is the same protein as NAIL. *Board Decision* at 4. A monoclonal antibody is an antibody that is mass produced in the laboratory from a single clone and that recognizes only one antigen. Monoclonal antibodies are useful as probes for specifically identifying and targeting a particular kind of cell.

Valiante teaches that "[t]he DNA and protein sequences for the receptor p38 may be obtained by resort to conventional methodologies known to one of skill in the art." '690 Patent col.7 ll.49–51.

For example, the receptor may be isolated by immunoprecipitation using the mAb C1.7. Alternatively, the receptor

may be obtained by prokaryotic expression cloning, using the lambda phage gtl1, which is described in detail in Sambrook et al, *Molecular Cloning, A Laboratory Manual*, 2d edit., Cold Spring Harbor, N.Y. (1989), pp. 2.43–2.84, incorporated by reference herein.

Additionally, as described in Example 12 below, the DNA sequence encoding the receptor can be obtained by the "panning" technique of screening a human NK cell library by eukaryotic expression cloning, of which several are known. Briefly, plasmids are constructed containing random sequences of a human NK cell library which are obtained by restriction digestion. Such libraries may be made by conventional techniques or may be available commercially.

Suitable cells, preferably mammalian cells, such as COS–1 cells, are transfected with the plasmids and the mAb C1.7 antibody employed to identify transfectants containing the receptor after repeated rounds of panning. The receptor insert in these cells is then identified and sequenced by conventional techniques, such as overlapping deletion fragments [Sambrook et al. cited above]. Other known techniques may also be employed to sequence the receptor and/or the mAb C1.7.

Id. at col.7 l.51–col.8 l.7. Example 12 of Valiante's patent further describes a five-step cloning protocol for "isolating and identifying the p38 receptor." *Id.* at col.18 l.6–col.19 l.28. Valiante discloses neither the amino acid sequence of p38 recognized by mAb C1.7 nor the polynucleotide sequence that encodes p38. Sambrook, incorporated by reference (as cited above) in Valiante, describes methods for molecular cloning. Sambrook does not discuss how to clone any particular gene, but provides detailed instructions on cloning materials and techniques.

The Mathew reference discloses a cell surface receptor protein called 2B4 “expressed on all NK . . . cells.” Mathew at 5328. Mathew discloses that 2B4 is involved in activating mouse NK cells, and further teaches the “chromosomal mapping, cloning, expression, and molecular characterization of the 2B4 gene.” *Id.* at 5329. Further, Mathew teaches a monoclonal antibody, mAb 2B4, specific to 2B4, and a detailed cloning protocol for obtaining the sequence of the gene that codes for the 2B4 protein. *Id.* at 5328–330. The Board found that Mathew’s signaling molecule 2B4 is the murine (mouse) version of Valiante’s p38. *Board Decision* at 5. The Board viewed Mathew’s teachings to be “cumulative to the teachings in Valiante and Sambrook and merely . . . exemplary of how routine skill in the art can be utilized to clone and sequence the cDNA of a similar polypeptide.” *Id.*

The Board found as a factual matter that appellants used conventional techniques “such as those outlined in Sambrook” to isolate and sequence the gene that codes for NAIL. *Id.* The Board also found that appellants’ claimed DNA sequence is “isolated from a cDNA library . . . using the commercial monoclonal antibody C1.7 . . . disclosed by Valiante.” *Id.* With regard to the amino acid sequence referred to as SEQ ID NO:2, the Board found that

Valiante’s disclosure of the polypeptide p38, and a detailed method of isolating its DNA, including disclosure of a specific probe to do so, i.e., mAb C1.7, established Valiante’s possession of p38’s amino acid sequence and provided a reasonable expectation of success in obtaining a polynucleotide encoding p38, a polynucleotide within the scope of Appellants’ claim 73. (See Valiante, col.7, 1.48 to col.8, 1.7.)

Id. at 6. Because of NAIL’s important role in the human immune response, the Board

further found that “one of ordinary skill in the art would have recognized the value of isolating NAIL cDNA, and would have been motivated to apply conventional methodologies, such as those disclosed in Sambrook and utilized in Valiante, to do so.” *Id.* at 6–7.

Based on these factual findings, the Board turned to the legal question of obviousness under § 103. Invoking the Supreme Court’s decision in *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398, 127 S.Ct. 1727, 167 L.Ed.2d 705 (2007), the Board concluded that appellants’ claim was “‘the product not of innovation but of ordinary skill and common sense,’ leading us to conclude NAIL cDNA is not patentable as it would have been obvious to isolate it.” *Board Decision* at 9 (citing *KSR*, 550 U.S. at 421, 127 S.Ct. 1727).

Appellants appeal the Board’s decisions both as to obviousness and written description. This court has jurisdiction under 28 U.S.C. § 1295(a)(4) and 35 U.S.C. § 141.

III.

[1] This court reviews the Board’s factual findings for lack of substantial evidence, and its legal conclusions without deference. *In re Gartside*, 203 F.3d 1305, 1315 (Fed.Cir.2000).

[2–4] Obviousness is a question of law based on underlying findings of fact. An analysis of obviousness must be based on several factual inquiries: (1) the scope and content of the prior art; (2) the differences between the prior art and the claims at issue; (3) the level of ordinary skill in the art at the time the invention was made; and (4) objective evidence of nonobviousness, if any. *See Graham v. John Deere Co.*, 383 U.S. 1, 17–18, 86 S.Ct. 684, 15 L.Ed.2d 545 (1966). The teachings of a prior art reference are underlying factual questions in the obviousness inquiry. *See*

Para-Ordnance Mfg., Inc. v. SGS Imp. Int'l, Inc., 73 F.3d 1085, 1088 (Fed.Cir. 1995).

A.

As a factual matter, the Board concluded that appellants' methodology of isolating NAIL DNA was essentially the same as the methodologies and teachings of Valiante and Sambrook. Appellants charge that the record does not contain substantial evidence to support this Board conclusion.

This emphasis on similarities or differences in methods of deriving the NAIL DNA misses the main point of this obviousness question. Of note, the record nowhere suggests that the technique in Valiante's Example 12 for isolating NAIL (p38) DNA, even if slightly different than the technique disclosed in the claimed invention, would not yield the same polynucleotide claimed in claim 73. Stated directly, the record shows repeatedly that Valiante's Example 12 produces for any person of ordinary skill in this art the claimed polynucleotide.

More to the point, however, any putative difference in Valiante's/Sambrook's and appellants' *processes* does not directly address the obviousness of representative claim 73, which claims a genus of *polynucleotides*. The difference between Valiante's and the application's techniques might be directly relevant to obviousness in this case if Kubin and Goodwin had claimed a method of DNA cloning or isolation. But they did not. Appellants claim a gene sequence. Accordingly, the obviousness inquiry requires this court to review the Board's decision that the claimed sequence, not appellants' unclaimed cloning technique, is obvious in light of the abundant prior art.

[5] In any event, this court determines that the Board had substantial evidence to conclude that appellants used conventional

techniques, as taught in Valiante and Sambrook, to isolate a gene sequence for NAIL. In particular, appellants' arguments that Valiante and Sambrook are deficient because they do not provide "any guidance for the preparation of cell culture that will serve as a useful source of mRNA for the preparation of a cDNA library," Appellants' Br. 34, are diminished by appellants' own disclosure:

A "nucleotide sequence" refers to a polynucleotide molecule in the form of a separate fragment or as a component of a larger nucleic acid construct. The nucleic acid molecule has been derived from DNA or RNA isolated at least once in substantially pure form and in a quantity or concentration enabling identification, manipulation, and recovery of its component nucleotide sequences by *standard biochemical methods (such as those outlined in Sambrook et al., Molecular Cloning: A Laboratory Manual, 2nd ed., Cold Spring Harbor Laboratory, Cold Spring Harbor, N.Y. (1989))*.

'859 Application at 16-17 (emphasis added). Thus, Kubin and Goodwin cannot represent to the public that their claimed gene sequence can be derived and isolated by "standard biochemical methods" discussed in a well-known manual on cloning techniques, while at the same time discounting the relevance of that very manual to the obviousness of their claims. For this reason as well, substantial evidence supports the Board's factual finding that "[a]ppellants employed conventional methods, 'such as those outlined in Sambrook,' to isolate a cDNA encoding NAIL and determine the cDNA's full nucleotide sequence (SEQ NOS: 1 & 3)." *Board Decision* at 5.

In a similar vein, this court reviews the Board's reference to the teachings of Mathew and the connection between Mathew's 2B4 and Valiante's p38 proteins.

As an initial point, the Board referenced Mathew only as cumulative of Sambrook and Valiante. Therefore, the Board's obviousness analysis does not explicitly rely on Mathew at all. Instead the Board observed that Mathew is "exemplary of how routine skill in the art can be utilized to clone and sequence the cDNA of a similar polypeptide." *Id.* In that connection, the record shows that a researcher of ordinary skill in this art would have recognized that both Valiante and Mathew are indisputably focused on regulation of NK cells—Mathew with regard to mice and Valiante with regard to humans. Like Valiante's Example 12, Mathew discusses a detailed protocol for identifying, isolating, and cloning cDNA encoding 2B4, which was later discovered to be the murine equivalent of Valiante's p38 and appellants' NAIL protein. Moreover, Mathew expressly states that his genomic DNA blot analysis "identified a human homologue of the 2B4 gene." Mathew at 5333. In sum, substantial evidence supports the Board's conclusion that Mathew reinforces the relative ease of deriving the claimed sequence following the teachings of the prior art.

[6] This court notes that Mathew contains some data that "suggests that [the] 2B4 gene is not expressed in humans." *Id.* This part of the record, however, does not undermine the Board's correct conclusion that Mathew does not "teach away" from combining its teachings with Valiante. "A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant." *In re Gurley*, 27 F.3d 551, 553 (Fed.Cir.1994). According to Mathew, "[i]t appears . . . that the 2B4 gene is somewhat conserved during evolution." Mathew at 5335. Mathew's quasi-agnostic stance toward the existence of a human homologue of the 2B4 gene cannot fairly

be seen as dissuading one of ordinary skill in the art from combining Mathew's teachings with those of Valiante. Rather, Mathew's disclosure, in light of Valiante's teachings regarding the p38 protein and its role in NK cell activation, would have aroused a skilled artisan's curiosity to isolate the gene coding for p38. Thus, the record supplies ample evidence to support the Board's finding that Mathew "exemplifies how the cDNA encoding 2B4, the mouse version of Valiante's p38 expressed on all NK cells, can be isolated and sequenced." *Board Decision* at 10.

This court also observes that the Board had no obligation to predicate its obviousness finding on factual findings regarding a prior art teaching of NAIL's binding to the CD48 protein. Even if no prior art of record explicitly discusses the "wherein the polypeptide binds CD48" aspect of claim 73, the Kubin-Goodwin application itself instructs that CD48 binding is not an additional requirement imposed by the claims on the NAIL protein, but rather a property necessarily present in NAIL. *See, e.g.*, '859 Application at 1, 8 (describing CD48 as NAIL's "counterstructure"). Because this court sustains, under substantial evidence review, the Board's finding that Valiante's p38 is the same protein as appellant's NAIL, Valiante's teaching to obtain cDNA encoding p38 also necessarily teaches one to obtain cDNA of NAIL that exhibits the CD48 binding property. *See, e.g., Gen. Elec. Co. v. Jewel Incandescent Lamp Co.*, 326 U.S. 242, 249, 66 S.Ct. 81, 90 L.Ed. 43 (1945) ("It is not invention to perceive that the product which others had discovered had qualities they failed to detect."); *In re Wiseman*, 596 F.2d 1019, 1023 (CCPA 1979) (rejecting the notion that "a structure suggested by the prior art, and, hence, potentially in the possession of the public, is patentable . . . because it also possesses an inherent, but hitherto unknown, function which [paten-

tees] claim to have discovered. This is not the law. A patent on such a structure would remove from the public that which is in the public domain by virtue of its inclusion in, or obviousness from, the prior art.”).

B.

The instant case also requires this court to consider the Board’s application of this court’s early assessment of obviousness in the context of classical biotechnological inventions, specifically *In re Deuel*, 51 F.3d 1552 (Fed.Cir.1995). In *Deuel*, this court reversed the Board’s conclusion that a prior art reference teaching a method of gene cloning, together with a reference disclosing a partial amino acid sequence of a protein, rendered DNA molecules encoding the protein obvious. *Id.* at 1559. In reversing the Board, this court in *Deuel* held that “knowledge of a protein does not give one a conception of a particular DNA encoding it.” *Id.* Further, this court stated that “obvious to try” is an inappropriate test for obviousness.

[T]he existence of a general method of isolating cDNA or DNA molecules is essentially irrelevant to the question whether the specific molecules themselves would have been obvious, in the absence of other prior art that suggests the claimed DNAs. . . . “Obvious to try” has long been held not to constitute obviousness. A general incentive does not make obvious a particular result, nor does the existence of techniques by which those efforts can be carried out.

Id. (internal citations omitted) (emphases added). Thus, this court must examine *Deuel*’s effect on the Board’s conclusion that Valiante’s teaching of the NAIL protein, combined with Valiante’s/Sam brook’s teaching of a method to isolate the gene sequence that codes for NAIL, renders claim 73 obvious.

With regard to *Deuel*, the Board addressed directly its application in this case. In particular, the Board observed that the Supreme Court in *KSR* cast doubts on this court’s application of the “obvious to try” doctrine:

To the extent *Deuel* is considered relevant to this case, we note the Supreme Court recently cast doubt on the viability of *Deuel* to the extent the Federal Circuit rejected an “obvious to try” test. *See KSR Int’l Co. v. Teleflex Inc.*, [550 U.S. 398], 127 S.Ct. 1727, 1737–38, 1740–41 [167 L.Ed.2d 705], 82 U.S.P.Q.2d 1385, 1394, 1396 (2007) (citing *Deuel*, 51 F.3d at 1559). Under *KSR*, it’s now apparent “obvious to try” may be an appropriate test in more situations than we previously contemplated.

Board Decision at 8. Insofar as *Deuel* implies the obviousness inquiry cannot consider that the combination of the claim’s constituent elements was “obvious to try,” the Supreme Court in *KSR* unambiguously discredited that holding. In fact, the Supreme Court expressly invoked *Deuel* as a source of the discredited “obvious to try” doctrine. The *KSR* Court reviewed this court’s rejection, based on *Deuel*, of evidence showing that a particular combination of prior art elements was obvious because it would have been obvious to one of ordinary skill in the art to attempt such a combination:

The only declaration offered by *KSR*—a declaration by its Vice President of Design Engineering, Larry Willemsen—did not go to the ultimate issue of motivation to combine prior art, i.e. whether one of ordinary skill in the art would have been motivated to attach an electronic control to the support bracket of the assembly disclosed by Asano. Mr. Willemsen did state that an electronic control “could have been” mounted on the support bracket of a pedal assembly.

(Willemsen Decl. at P33, 36, 39.) Such testimony is not sufficient to support a finding of obviousness, however. See, e.g., *In re Deuel*, 51 F.3d 1552, 1559 (Fed.Cir.1995) (“‘Obvious to try’ has long been held not to constitute obviousness.”).

Teleflex, Inc. v. KSR Int’l Co., 119 Fed. Appx. 282, 289 (Fed.Cir.2005). The Supreme Court repudiated as “error” the *Deuel* restriction on the ability of a skilled artisan to combine elements within the scope of the prior art:

The same constricted analysis led the Court of Appeals to conclude, in error, that a patent claim cannot be proved obvious merely by showing that the combination of elements was “obvious to try.” When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance *the fact that a combination was obvious to try might show that it was obvious under § 103.*

KSR, 550 U.S. at 421, 127 S.Ct. 1727 (internal citation omitted) (emphasis added).

The Supreme Court’s admonition against a formalistic approach to obviousness in this context actually resurrects this court’s own wisdom in *In re O’Farrell*, which predates the *Deuel* decision by some seven years. This court in *O’Farrell* cautioned that “obvious to try” is an incantation whose meaning is often misunderstood:

It is true that this court and its predecessors have repeatedly emphasized that “obvious to try” is not the standard under § 103. However, the meaning of this maxim is sometimes lost. Any in-

vention that would in fact have been obvious under § 103 would also have been, in a sense, obvious to try. The question is: when is an invention that was obvious to try nevertheless nonobvious?

In re O’Farrell, 853 F.2d 894, 903 (Fed. Cir.1988). To differentiate between proper and improper applications of “obvious to try,” this court outlined two classes of situations where “obvious to try” is erroneously equated with obviousness under § 103. In the first class of cases,

what would have been “obvious to try” would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful.

Id. In such circumstances, where a defendant merely throws metaphorical darts at a board filled with combinatorial prior art possibilities, courts should not succumb to hindsight claims of obviousness. The inverse of this proposition is succinctly encapsulated by the Supreme Court’s statement in *KSR* that where a skilled artisan merely pursues “known options” from a “finite number of identified, predictable solutions,” obviousness under § 103 arises. 550 U.S. at 421, 127 S.Ct. 1727.

The second class of *O’Farrell*’s impermissible “obvious to try” situations occurs where

what was “obvious to try” was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it.

853 F.2d at 903. Again, *KSR* affirmed the logical inverse of this statement by stating

that § 103 bars patentability unless “the improvement is more than the predictable use of prior art elements according to their established functions.” 550 U.S. at 417, 127 S.Ct. 1727.

This court in *O’Farrell* found the patentee’s claims obvious because the Board’s rejection of the patentee’s claims had not presented either of the two common “obvious to try” pitfalls. Specifically, this court observed that an obviousness finding was appropriate where the prior art “contained *detailed enabling methodology* for practicing the claimed invention, a suggestion to modify the prior art to practice the claimed invention, and evidence suggesting that it would be successful.” 853 F.2d at 902 (emphasis added). Responding to concerns about uncertainty in the prior art influencing the purported success of the claimed combination, this court stated: “[o]bviousness does not require absolute predictability of success . . . *all that is required is a reasonable expectation of success.*” *Id.* at 903–04 (emphasis added). The Supreme Court in *KSR* reinvigorated this perceptive analysis.

KSR and *O’Farrell* directly implicate the instant case. Appellants’ claim 73 recites a genus of isolated nucleic acid molecules encoding the NAIL protein. As found by the Board, the Valiante reference discloses the very protein of appellants’ interest—“p38” as per Valiante. *Board Decision* at 4. Valiante discloses a monoclonal antibody mAb C1.7 that is specific for p38/NAIL, and further teaches a five-step protocol for cloning nucleic acid molecules encoding p38/NAIL using mAb C1.7. *Id.* In fact, while stating that “[t]he DNA and protein sequences for the receptor p38 may be obtained by resort to conventional methodologies known to one of skill in the art,” ‘690 Patent at col.7 ll.49–51, Valiante cites to the *very same* cloning manual, Sambrook, cited by Kubin and Goodwin for their proposition that the gene sequence is identified and recovered “by standard bio-

chemical methods.” ‘859 Application at 16. Moreover, the record strongly reinforces (and appellants apparently find no room to dispute) the Board’s factual finding that one of ordinary skill would have been motivated to isolate NAIL cDNA, given Valiante’s teaching that p38 is “expressed by virtually all human NK cells and thus plays a role in the immune response.” *Board Decision* at 6. The record shows that the prior art teaches a protein of interest, a motivation to isolate the gene coding for that protein, and illustrative instructions to use a monoclonal antibody specific to the protein for cloning this gene. Therefore, the claimed invention is “the product not of innovation but of ordinary skill and common sense.” *KSR*, 550 U.S. at 421, 127 S.Ct. 1727. Or stated in the familiar terms of this court’s longstanding case law, the record shows that a skilled artisan would have had a resoundingly “reasonable expectation of success” in deriving the claimed invention in light of the teachings of the prior art. *See O’Farrell*, 853 F.2d at 904.

This court also declines to cabin *KSR* to the “predictable arts” (as opposed to the “unpredictable art” of biotechnology). In fact, this record shows that one of skill in this advanced art would find these claimed “results” profoundly “predictable.” The record shows the well-known and reliable nature of the cloning and sequencing techniques in the prior art, not to mention the readily knowable and obtainable structure of an identified protein. Therefore this court cannot deem irrelevant the ease and predictability of cloning the gene that codes for that protein. This court cannot, in the face of *KSR*, cling to formalistic rules for obviousness, customize its legal tests for specific scientific fields in ways that deem entire classes of prior art teachings irrelevant, or discount the significant abilities of artisans of ordinary skill in an advanced area of art. *See In re Durden*,

763 F.2d 1406, 1411 (Fed.Cir.1985) (“Our function is to apply, in each case, § 103 as written to the facts of disputed issues, not to generalize or make rules for other cases which are unforeseeable.”). As this court’s predecessor stated in *In re Papesch*, “[t]he problem of ‘obviousness’ under section 103 in determining the patentability of new and useful chemical compounds . . . is not really a problem in chemistry or pharmacology or in any other related field of science such as biology, biochemistry, pharmacodynamics, ecology, or others yet to be conceived. It is a problem of patent law.” 315 F.2d 381, 386 (CCPA 1963).

The record in this case shows that Valiante did not explicitly supply an amino acid sequence for NAIL or a polynucleotide sequence for the NAIL gene. In that sense, Kubin and Goodwin’s disclosure represents some minor advance in the art. But “[g]ranting patent protection to advances that would occur in the ordinary course without real innovation retards progress.” *KSR*, 550 U.S. at 419, 127 S.Ct. 1727. “Were it otherwise patents might stifle, rather than promote, the progress of useful arts.” *Id.* at 427, 127 S.Ct. 1727. In light of the concrete, specific teachings of Sambrook and Valiante, artisans in this field, as found by the Board in its expertise, had every motivation to seek and every reasonable expectation of success in achieving the sequence of the claimed invention. In that sense, the claimed invention was reasonably expected in light of the prior art and “obvious to try.” See *Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 520 F.3d 1358, 1364 (Fed.Cir.2008) (“*KSR* posits a situation with a finite, and in the context of the art, small or easily traversed, number of options that would convince an ordinarily skilled artisan of obviousness.”). These references, which together teach a protein identical to NAIL, a commercially available monoclonal antibody specific for NAIL, and explicit instructions for obtain-

ing the DNA sequence for NAIL, are not analogous to prior art that gives “no direction as to which of many possible choices is likely to be successful” or “only general guidance as to the particular form of the claimed invention or how to achieve it.” *O’Farrell*, 853 F.2d at 903. As the Board found, the prior art here provides a “reasonable expectation of success” for obtaining a polynucleotide within the scope of claim 73, *Board Decision* at 6, which, “[f]or obviousness under § 103 [is] all that is required.” *O’Farrell*, 853 F.2d at 903. Thus, this court affirms the Board’s conclusion as to obviousness.

IV.

For the reasons stated above, the Board did not err in finding appellants’ claims obvious as a matter of law. Thus, this court need not address appellants’ contention that the Board erred in finding its claims invalid under § 112 ¶ 1. Accordingly, this court affirms the decision of the Board.

AFFIRMED.

COSTS

Each party shall bear its own costs.



**PALMYRA PACIFIC SEAFOODS,
L.L.C., Palmyra Pacific Enterprises,
L.L.C., PPE Limited Partnership, and
Frank Sorba, Plaintiffs-Appellants,**

v.

UNITED STATES, Defendant-Appellee.

No. 2008-5058.

United States Court of Appeals,
Federal Circuit.

April 9, 2009.

Background: Commercial fishing entities brought action against the United States

Westlaw.

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Weekly Fed. S 248

(Cite as: 127 S.Ct. 1727)



KSR Intern. Co. v. Teleflex Inc.
U.S., 2007.

Supreme Court of the United States
KSR INTERNATIONAL CO., Petitioner,

v.

TELEFLEX INC. et al.

No. 04-1350.

Argued Nov. 28, 2006.

Decided April 30, 2007.

Background: Exclusive licensee of patent for position-adjustable vehicle pedal assembly sued competitor for infringement. The United States District Court for the Eastern District of Michigan, 298 F.Supp.2d 581, granted summary judgment for competitor on the ground of obviousness. Licensee appealed. The United States Court of Appeals for the Federal Circuit, 119 Fed.Appx. 282, reversed. Certiorari was granted.

Holding: The Supreme Court, Justice Kennedy, held that patent was invalid as obvious.

Reversed and remanded.

West Headnotes

[1] Patents 291 26(1.1)

291 Patents

291II Patentability

291II(A) Invention; Obviousness

291k26 Combination

291k26(1.1) k. Use of Old or Well-Known Elements. Most Cited Cases
Patent claiming the combination of elements of prior art is obvious if the improvement is no more than the predictable use of prior art elements according to their established functions. 35 U.S.C.A. § 103.

[2] Patents 291 26(1.1)

291 Patents

291II Patentability

291II(A) Invention; Obviousness

291k26 Combination

291k26(1.1) k. Use of Old or Well-Known Elements. Most Cited Cases

Patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art. 35 U.S.C.A. § 103.

[3] Patents 291 16.5(1)

291 Patents

291II Patentability

291II(A) Invention; Obviousness

291k16.5 State of Prior Art and Advancement Therein

291k16.5(1) k. In General. Most Cited Cases

In determining whether subject matter of patent claim is obvious, neither the particular motivation nor the avowed purpose of patentee controls; what matters is the objective reach of the claim. 35 U.S.C.A. § 103.

[4] Patents 291 16.5(4)

291 Patents

291II Patentability

291II(A) Invention; Obviousness

291k16.5 State of Prior Art and Advancement Therein

291k16.5(4) k. Remedying Defects or Solving Problems. Most Cited Cases

Patent's subject matter can be proved obvious by noting that there existed at time of invention a known problem for which there was an obvious solution encompassed by patent's claims. 35 U.S.C.A. § 103.

[5] Patents 291 16(3)

291 Patents

291II Patentability

291II(A) Invention; Obviousness
 291k16 Invention and Obviousness in
 General

291k16(3) k. View of Person Skilled in
 Art. Most Cited Cases

Patents 291 ⚙️16.5(4)

291 Patents

291II Patentability

291II(A) Invention; Obviousness

291k16.5 State of Prior Art and Advance-
 ment Therein

291k16.5(4) k. Remediating Defects or
 Solving Problems. Most Cited Cases

In determining whether patent combining known elements is obvious, question is not whether the combination was obvious to the patentee but whether the combination was obvious to a person with ordinary skill in the art; under correct analysis, any need or problem known in the field of endeavor at the time of invention and addressed by the patent can provide reason for combining the elements in the manner claimed. 35 U.S.C.A. § 103.

[6] Patents 291 ⚙️16.5(4)

291 Patents

291II Patentability

291II(A) Invention; Obviousness

291k16.5 State of Prior Art and Advance-
 ment Therein

291k16.5(4) k. Remediating Defects or
 Solving Problems. Most Cited Cases

Patents 291 ⚙️17(1)

291 Patents

291II Patentability

291II(A) Invention; Obviousness

291k17 Nature and Degree of Skill In-
 volved

291k17(1) k. In General. Most Cited
 Cases

When there is design need or market pressure to solve a problem and there are finite number of iden-

tified, predictable solutions, person of ordinary skill has good reason to pursue the known options within his or her technical grasp, and if this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense; in that instance, the fact that a combination was obvious to try might show that patent for it was obvious. 35 U.S.C.A. § 103.

[7] Patents 291 ⚙️16.22

291 Patents

291II Patentability

291II(A) Invention; Obviousness

291k16.22 k. Automobiles and Vehicles.

Most Cited Cases

Patent claim disclosing position-adjustable pedal assembly with electronic pedal position sensor attached to support member of pedal assembly was invalid as obvious, in view of patent for adjustable pedal with a fixed pivot, and patent teaching a solution to wire chafing problems, namely locating the sensor on support structure; it was obvious to person of ordinary skill in the art to combine first patent with pivot-mounted pedal position sensor. 35 U.S.C.A. § 103.

[8] Patents 291 ⚙️323.2(2)

291 Patents

291XII Infringement

291XII(C) Suits in Equity

291k323 Final Judgment or Decree

291k323.2 Summary Judgment

291k323.2(2) k. Presence or Ab-
 sence of Fact Issues. Most Cited Cases

Where content of prior art, scope of patent claim, and level of ordinary skill in the art are not in material dispute, and obviousness of claim is apparent in light of these factors, summary judgment is appropriate. 35 U.S.C.A. § 103. c

Patents 291 ⚙️328(2)

291 Patents

291XIII Decisions on the Validity, Construction,

and Infringement of Particular Patents

291k328 Patents Enumerated

291k328(2) k. Original Utility. Most

Cited Cases

5,010,782, 5,063,811, 5,241,936, 5,385,068,
5,460,061, 5,819,593, 6,151,976. Cited as Prior Art.

Patents 291 ↪ 328(2)

291 Patents

291XIII Decisions on the Validity, Construction,
and Infringement of Particular Patents

291k328 Patents Enumerated

291k328(2) k. Original Utility. Most

Cited Cases

6,109,241. Cited.

Patents 291 ↪ 328(2)

291 Patents

291XIII Decisions on the Validity, Construction,
and Infringement of Particular Patents

291k328 Patents Enumerated

291k328(2) k. Original Utility. Most

Cited Cases

6,237,565. Invalid.

***1728 Syllabus** ^{FN*}

FN* The syllabus constitutes no part of the opinion of the Court but has been prepared by the Reporter of Decisions for the convenience of the reader. See *United States v. Detroit Timber & Lumber Co.*, 200 U.S. 321, 337, 26 S.Ct. 282, 50 L.Ed. 499.

To control a conventional automobile's speed, the driver depresses or releases the gas pedal, which interacts with the throttle via a cable or other mechanical link. Because the pedal's position in the footwell normally cannot be adjusted, a driver wishing to be closer or farther from it must either reposition himself in the seat *1729 or move the seat, both of which can be imperfect solutions for smaller drivers in cars with deep footwells. This prompted inventors to design and patent pedals that could be adjusted to change their locations. The Asano patent re-

veals a support structure whereby, when the pedal location is adjusted, one of the pedal's pivot points stays fixed. Asano is also designed so that the force necessary to depress the pedal is the same regardless of location adjustments. The Redding patent reveals a different, sliding mechanism where both the pedal and the pivot point are adjusted.

In newer cars, computer-controlled throttles do not operate through force transferred from the pedal by a mechanical link, but open and close valves in response to electronic signals. For the computer to know what is happening with the pedal, an electronic sensor must translate the mechanical operation into digital data. Inventors had obtained a number of patents for such sensors. The so-called '936 patent taught that it was preferable to detect the pedal's position in the pedal mechanism, not in the engine, so the patent disclosed a pedal with an electronic sensor on a pivot point in the pedal assembly. The Smith patent taught that to prevent the wires connecting the sensor to the computer from chafing and wearing out, the sensor should be put on a fixed part of the pedal assembly rather than in or on the pedal's footpad. Inventors had also patented self-contained modular sensors, which can be taken off the shelf and attached to any mechanical pedal to allow it to function with a computer-controlled throttle. The '068 patent disclosed one such sensor. Chevrolet also manufactured trucks using modular sensors attached to the pedal support bracket, adjacent to the pedal and engaged with the pivot shaft about which the pedal rotates. Other patents disclose electronic sensors attached to adjustable pedal assemblies. For example, the Rixon patent locates the sensor in the pedal footpad, but is known for wire chafing.

After petitioner KSR developed an adjustable pedal system for cars with cable-actuated throttles and obtained its '976 patent for the design, General Motors Corporation (GMC) chose KSR to supply adjustable pedal systems for trucks using computer-controlled throttles. To make the '976 pedal compatible with the trucks, KSR added a modular

sensor to its design. Respondents (Teleflex) hold the exclusive license for the Engelgau patent, claim 4 of which discloses a position-adjustable pedal assembly with an electronic pedal position sensor attached a fixed pivot point. Despite having denied a similar, broader claim, the U.S. Patent and Trademark Office (PTO) had allowed claim 4 because it included the limitation of a fixed pivot position, which distinguished the design from Redding's. Asano was neither included among the Engelgau patent's prior art references nor mentioned in the patent's prosecution, and the PTO did not have before it an adjustable pedal with a fixed pivot point. After learning of KSR's design for GMC, Teleflex sued for infringement, asserting that KSR's pedal system infringed the Engelgau patent's claim 4. KSR countered that claim 4 was invalid under § 103 of the Patent Act, which forbids issuance of a patent when "the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art."

Graham v. John Deere Co. of Kansas City, 383 U.S. 1, 17-18, 86 S.Ct. 684, 15 L.Ed.2d 545, set out an objective analysis for applying § 103: "[T]he scope and content of the prior art are ... determined; differences between the prior art and the *1730 claims at issue are ... ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background the obviousness or nonobviousness of the subject matter is determined. Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented." While the sequence of these questions might be reordered in any particular case, the factors define the controlling inquiry. However, seeking to resolve the obviousness question with more uniformity and consistency, the Federal Circuit has employed a "teaching, suggestion, or motivation" (TSM) test, under which a patent claim is only proved obvious if the prior art, the problem's

nature, or the knowledge of a person having ordinary skill in the art reveals some motivation or suggestion to combine the prior art teachings.

The District Court granted KSR summary judgment. After reviewing pedal design history, the Engelgau patent's scope, and the relevant prior art, the court considered claim 4's validity, applying *Graham's* framework to determine whether under summary-judgment standards KSR had demonstrated that claim 4 was obvious. The court found "little difference" between the prior art's teachings and claim 4: Asano taught everything contained in the claim except using a sensor to detect the pedal's position and transmit it to a computer controlling the throttle. That additional aspect was revealed in, e.g., the '068 patent and Chevrolet's sensors. The court then held that KSR satisfied the TSM test, reasoning (1) the state of the industry would lead inevitably to combinations of electronic sensors and adjustable pedals, (2) Rixon provided the basis for these developments, and (3) Smith taught a solution to Rixon's chafing problems by positioning the sensor on the pedal's fixed structure, which could lead to the combination of a pedal like Asano with a pedal position sensor.

Reversing, the Federal Circuit ruled the District Court had not applied the TSM test strictly enough, having failed to make findings as to the specific understanding or principle within a skilled artisan's knowledge that would have motivated one with no knowledge of the invention to attach an electronic control to the Asano assembly's support bracket. The Court of Appeals held that the District Court's recourse to the nature of the problem to be solved was insufficient because, unless the prior art references addressed the precise problem that the patentee was trying to solve, the problem would not motivate an inventor to look at those references. The appeals court found that the Asano pedal was designed to ensure that the force required to depress the pedal is the same no matter how the pedal is adjusted, whereas Engelgau sought to provide a simpler, smaller, cheaper adjustable electronic pedal.

The Rixon pedal, said the court, suffered from chafing but was not designed to solve that problem and taught nothing helpful to Engelgau's purpose. Smith, in turn, did not relate to adjustable pedals and did not necessarily go to the issue of motivation to attach the electronic control on the pedal assembly's support bracket. So interpreted, the court held, the patents would not have led a person of ordinary skill to put a sensor on an Asano-like pedal. That it might have been obvious to try that combination was likewise irrelevant. Finally, the court held that genuine issues of material fact precluded summary judgment.

Held: The Federal Circuit addressed the obviousness question in a narrow, rigid manner that is inconsistent with § 103 and this Court's precedents. KSR provided *1731 convincing evidence that mounting an available sensor on a fixed pivot point of the Asano pedal was a design step well within the grasp of a person of ordinary skill in the relevant art and that the benefit of doing so would be obvious. Its arguments, and the record, demonstrate that the Engelgau patent's claim 4 is obvious. Pp. 1739 - 1746.

1. *Graham* provided an expansive and flexible approach to the obviousness question that is inconsistent with the way the Federal Circuit applied its TSM test here. Neither § 103's enactment nor *Graham's* analysis disturbed the Court's earlier instructions concerning the need for caution in granting a patent based on the combination of elements found in the prior art. See *Great Atlantic & Pacific Tea Co. v. Supermarket Equipment Corp.*, 340 U.S. 147, 152, 71 S.Ct. 127, 95 L.Ed. 162. Such a combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results. See, e.g., *United States v. Adams*, 383 U.S. 39, 50-52, 86 S.Ct. 708, 15 L.Ed.2d 572. When a work is available in one field, design incentives and other market forces can prompt variations of it, either in the same field or in another. If a person of ordinary skill in the art can implement a predictable variation, and would see

the benefit of doing so, § 103 likely bars its patentability. Moreover, if a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond that person's skill. A court must ask whether the improvement is more than the predictable use of prior-art elements according to their established functions. Following these principles may be difficult if the claimed subject matter involves more than the simple substitution of one known element for another or the mere application of a known technique to a piece of prior art ready for the improvement. To determine whether there was an apparent reason to combine the known elements in the way a patent claims, it will often be necessary to look to interrelated teachings of multiple patents; to the effects of demands known to the design community or present in the marketplace; and to the background knowledge possessed by a person having ordinary skill in the art. To facilitate review, this analysis should be made explicit. But it need not seek out precise teachings directed to the challenged claim's specific subject matter, for a court can consider the inferences and creative steps a person of ordinary skill in the art would employ. Pp. 1739 - 1741.

(b) The TSM test captures a helpful insight: A patent composed of several elements is not proved obvious merely by demonstrating that each element was, independently, known in the prior art. Although common sense directs caution as to a patent application claiming as innovation the combination of two known devices according to their established functions, it can be important to identify a reason that would have prompted a person of ordinary skill in the art to combine the elements as the new invention does. Inventions usually rely upon building blocks long since uncovered, and claimed discoveries almost necessarily will be combinations of what, in some sense, is already known. Helpful insights, however, need not become rigid and mandatory formulas. If it is so applied, the TSM test is

incompatible with this Court's precedents. The diversity of inventive pursuits and of modern technology counsels against confining the obviousness analysis by a formalistic conception of the words teaching, suggestion, and motivation, or by overemphasizing the importance of published articles and the explicit *1732 content of issued patents. In many fields there may be little discussion of obvious techniques or combinations, and market demand, rather than scientific literature, may often drive design trends. Granting patent protection to advances that would occur in the ordinary course without real innovation retards progress and may, for patents combining previously known elements, deprive prior inventions of their value or utility. Since the TSM test was devised, the Federal Circuit doubtless has applied it in accord with these principles in many cases. There is no necessary inconsistency between the test and the *Graham* analysis. But a court errs where, as here, it transforms general principle into a rigid rule limiting the obviousness inquiry. Pp. 1740 - 1741.

(c) The flaws in the Federal Circuit's analysis relate mostly to its narrow conception of the obviousness inquiry consequent in its application of the TSM test. The Circuit first erred in holding that courts and patent examiners should look only to the problem the patentee was trying to solve. Under the correct analysis, any need or problem known in the field and addressed by the patent can provide a reason for combining the elements in the manner claimed. Second, the appeals court erred in assuming that a person of ordinary skill in the art attempting to solve a problem will be led only to those prior art elements designed to solve the same problem. The court wrongly concluded that because Asano's primary purpose was solving the constant ratio problem, an inventor considering how to put a sensor on an adjustable pedal would have no reason to consider putting it on the Asano pedal. It is common sense that familiar items may have obvious uses beyond their primary purposes, and a person of ordinary skill often will be able to fit the teachings of multiple patents together like pieces of a puzzle.

Regardless of Asano's primary purpose, it provided an obvious example of an adjustable pedal with a fixed pivot point, and the prior art was replete with patents indicating that such a point was an ideal mount for a sensor. Third, the court erred in concluding that a patent claim cannot be proved obvious merely by showing that the combination of elements was obvious to try. When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill in the art has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. Finally, the court drew the wrong conclusion from the risk of courts and patent examiners falling prey to hindsight bias. Rigid preventative rules that deny recourse to common sense are neither necessary under, nor consistent with, this Court's case law. Pp. 1741 - 1743.

2. Application of the foregoing standards demonstrates that claim 4 is obvious. Pp. 1743 - 1746.

(a) The Court rejects Teleflex's argument that the Asano pivot mechanism's design prevents its combination with a sensor in the manner claim 4 describes. This argument was not raised before the District Court, and it is unclear whether it was raised before the Federal Circuit. Given the significance of the District Court's finding that combining Asano with a pivot-mounted pedal position sensor fell within claim 4's scope, it is apparent that Teleflex would have made clearer challenges if it intended to preserve this claim. Its failure to clearly raise the argument, and the appeals court's silence on the issue, lead this Court to accept the District Court's conclusion. Pp. 1743 - 1744.

*1733 (b) The District Court correctly concluded that when Engelgau designed the claim 4 subject matter, it was obvious to a person of ordinary skill in the art to combine Asano with a pivot-mounted pedal position sensor. There then was a marketplace creating a strong incentive to convert mech-

anical pedals to electronic pedals, and the prior art taught a number of methods for doing so. The Federal Circuit considered the issue too narrowly by, in effect, asking whether a pedal designer writing on a blank slate would have chosen both Asano and a modular sensor similar to the ones used in the Chevrolet trucks and disclosed in the '068 patent. The proper question was whether a pedal designer of ordinary skill in the art, facing the wide range of needs created by developments in the field, would have seen an obvious benefit to upgrading Asano with a sensor. For such a designer starting with Asano, the question was where to attach the sensor. The '936 patent taught the utility of putting the sensor on the pedal device. Smith, in turn, explained not to put the sensor on the pedal footpad, but instead on the structure. And from Rixon's known wire-chafing problems, and Smith's teaching that the pedal assemblies must not precipitate any motion in the connecting wires, the designer would know to place the sensor on a nonmoving part of the pedal structure. The most obvious such point is a pivot point. The designer, accordingly, would follow Smith in mounting the sensor there. Just as it was possible to begin with the objective to upgrade Asano to work with a computer-controlled throttle, so too was it possible to take an adjustable electronic pedal like Rixon and seek an improvement that would avoid the wire-chafing problem. Teleflex has not shown anything in the prior art that taught away from the use of Asano, nor any secondary factors to dislodge the determination that claim 4 is obvious. Pp. 1744 - 1746.

3. The Court disagrees with the Federal Circuit's holding that genuine issues of material fact precluded summary judgment. The ultimate judgment of obviousness is a legal determination. *Graham*, 383 U.S., at 17, 86 S.Ct. 684. Where, as here, the prior art's content, the patent claim's scope, and the level of ordinary skill in the art are not in material dispute and the claim's obviousness is apparent, summary judgment is appropriate. Pp. 1745 - 1746.

119 Fed.Appx. 282, reversed and remanded.

KENNEDY, J., delivered the opinion for a unanimous Court.

James W. Dabney, for petitioner.

Thomas G. Hungar, for the United States as amicus curiae, by special leave of the Court, supporting the petitioner.

Thomas C. Goldstein, for respondents.

John F. Duffy, Fried, Frank, Harris, Shriver & Jacobson LLP, Of Counsel, James W. Dabney, Counsel of Record, New York, New York, Stephen S. Rabinowitz, Henry C. Lebowitz, Mitchell E. Epner, Darcy M. Goddard, Fried, Frank, Harris, Shriver & Jacobson LLP, New York, New York, Attorneys for Petitioner.

Kenneth C. Bass, III, Robert G. Sterne, Sterne, Kessler Goldstein & Fox P.L.L.C., Washington, DC, Rodger D. Young, Steven Susser, David Poirier, Young & Susser, P.C., Southfield, Thomas C. Goldstein, Counsel of Record, Michael A. O'Shea, Garreth A. Sarosi, Christopher R. Pudelski, Sarah C. Rispin, Akin Gump Strauss Hauer & Feld, LLP, Washington, DC, Samuel J. Haidle, David M. LaPrairie, Howard & Howard, Attorneys, P.C., Bloomfield Hills, MI, Tracy L. Casadio, *1734 Elizabeth H. Rader, Akin Gump Strauss Hauer & Feld, LLP, Los Angeles, CA, Brief for the Respondents. For U.S. Supreme Court briefs, see: 2006 WL 2515631 (Pet.Brief) 2006 WL 2989549 (Resp.Brief) 2006 WL 3367870 (Reply.Brief) 2006 WL 3146709 (Resp.Supp.Brief)

Justice KENNEDY delivered the opinion of the Court.

Teleflex Incorporated and its subsidiary Technology Holding Company—both referred to here as Teleflex—sued KSR International Company for patent infringement. The patent at issue, United States Patent No. 6,237,565 B1, is entitled “Adjustable Pedal Assembly With Electronic Throttle Control.” Supplemental App. 1. The patentee is Steven J. Engelgau, and the patent is referred to as “the Engelgau patent.” Teleflex holds the exclusive license to the patent.

Claim 4 of the Engelgau patent describes a mechan-

ism for combining an electronic sensor with an adjustable automobile pedal so the pedal's position can be transmitted to a computer that controls the throttle in the vehicle's engine. When Teleflex accused KSR of infringing the Engelgau patent by adding an electronic sensor to one of KSR's previously designed pedals, KSR countered that claim 4 was invalid under the Patent Act, 35 U.S.C. § 103, because its subject matter was obvious.

Section 103 forbids issuance of a patent when “the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains.”

In *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 86 S.Ct. 684, 15 L.Ed.2d 545 (1966), the Court set out a framework for applying the statutory language of § 103, language itself based on the logic of the earlier decision in *Hotchkiss v. Greenwood*, 11 How. 248, 13 L.Ed. 683 (1851), and its progeny. See 383 U.S., at 15-17, 86 S.Ct. 684. The analysis is objective:

“Under § 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background the obviousness or nonobviousness of the subject matter is determined. Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented.” *Id.*, at 17-18, 86 S.Ct. 684.

While the sequence of these questions might be reordered in any particular case, the factors continue to define the inquiry that controls. If a court, or patent examiner, conducts this analysis and concludes the claimed subject matter was obvious, the claim is invalid under § 103.

Seeking to resolve the question of obviousness with more uniformity and consistency, the Court of Appeals for the Federal Circuit has employed an approach referred to by the parties as the “teaching, suggestion, or motivation” test (TSM test), under which a patent claim is only proved obvious if “some motivation or suggestion to combine the prior art teachings” can be found in the prior art, the nature of the problem, or the knowledge of a person having ordinary skill in the art. See, e.g., *Al-Site Corp. v. VSI Int'l, Inc.*, 174 F.3d 1308, 1323-1324 (C.A.Fed.1999). KSR challenges that *1735 test, or at least its application in this case. See 119 Fed.Appx. 282, 286-290 (C.A.Fed.2005). Because the Court of Appeals addressed the question of obviousness in a manner contrary to § 103 and our precedents, we granted certiorari, 547 U.S. ----, 126 S.Ct. 2965, 165 L.Ed.2d 949 (2006). We now reverse.

I

A

In car engines without computer-controlled throttles, the accelerator pedal interacts with the throttle via cable or other mechanical link. The pedal arm acts as a lever rotating around a pivot point. In a cable-actuated throttle control the rotation caused by pushing down the pedal pulls a cable, which in turn pulls open valves in the carburetor or fuel injection unit. The wider the valves open, the more fuel and air are released, causing combustion to increase and the car to accelerate. When the driver takes his foot off the pedal, the opposite occurs as the cable is released and the valves slide closed.

In the 1990's it became more common to install computers in cars to control engine operation. Computer-controlled throttles open and close valves in response to electronic signals, not through force transferred from the pedal by a mechanical link. Constant, delicate adjustments of air and fuel

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mixture are possible. The computer's rapid processing of factors beyond the pedal's position improves fuel efficiency and engine performance.

For a computer-controlled throttle to respond to a driver's operation of the car, the computer must know what is happening with the pedal. A cable or mechanical link does not suffice for this purpose; at some point, an electronic sensor is necessary to translate the mechanical operation into digital data the computer can understand.

Before discussing sensors further we turn to the mechanical design of the pedal itself. In the traditional design a pedal can be pushed down or released but cannot have its position in the footwell adjusted by sliding the pedal forward or back. As a result, a driver who wishes to be closer or farther from the pedal must either reposition himself in the driver's seat or move the seat in some way. In cars with deep footwells these are imperfect solutions for drivers of smaller stature. To solve the problem, inventors, beginning in the 1970's, designed pedals that could be adjusted to change their location in the footwell. Important for this case are two adjustable pedals disclosed in U.S. Patent Nos. 5,010,782 (filed July 28, 1989) (Asano) and 5,460,061 (filed Sept. 17, 1993) (Redding). The Asano patent reveals a support structure that houses the pedal so that even when the pedal location is adjusted relative to the driver, one of the pedal's pivot points stays fixed. The pedal is also designed so that the force necessary to push the pedal down is the same regardless of adjustments to its location. The Redding patent reveals a different, sliding mechanism where both the pedal and the pivot point are adjusted.

We return to sensors. Well before Engelgau applied for his challenged patent, some inventors had obtained patents involving electronic pedal sensors for computer-controlled throttles. These inventions, such as the device disclosed in U.S. Patent No. 5,241,936 (filed Sept. 9, 1991) ('936), taught that it was preferable to detect the pedal's position in the pedal assembly, not in the engine. The '936 patent

disclosed a pedal with an electronic sensor on a pivot point in the pedal assembly. U.S. Patent No. 5,063,811 (filed July 9, 1990) (Smith) taught that to prevent the *1736 wires connecting the sensor to the computer from chafing and wearing out, and to avoid grime and damage from the driver's foot, the sensor should be put on a fixed part of the pedal assembly rather than in or on the pedal's footpad.

In addition to patents for pedals with integrated sensors inventors obtained patents for self-contained modular sensors. A modular sensor is designed independently of a given pedal so that it can be taken off the shelf and attached to mechanical pedals of various sorts, enabling the pedals to be used in automobiles with computer-controlled throttles. One such sensor was disclosed in U.S. Patent No. 5,385,068 (filed Dec. 18, 1992) ('068). In 1994, Chevrolet manufactured a line of trucks using modular sensors "attached to the pedal support bracket, adjacent to the pedal and engaged with the pivot shaft about which the pedal rotates in operation." 298 F.Supp.2d 581, 589 (E.D.Mich.2003).

The prior art contained patents involving the placement of sensors on adjustable pedals as well. For example, U.S. Patent No. 5,819,593 (filed Aug. 17, 1995) (Rixon) discloses an adjustable pedal assembly with an electronic sensor for detecting the pedal's position. In the Rixon pedal the sensor is located in the pedal footpad. The Rixon pedal was known to suffer from wire chafing when the pedal was depressed and released.

This short account of pedal and sensor technology leads to the instant case.

B

KSR, a Canadian company, manufactures and supplies auto parts, including pedal systems. Ford Motor Company hired KSR in 1998 to supply an adjustable pedal system for various lines of automobiles with cable-actuated throttle controls. KSR developed an adjustable mechanical pedal for Ford

and obtained U.S. Patent No. 6,151,976 (filed July 16, 1999) ('976) for the design. In 2000, KSR was chosen by General Motors Corporation (GMC or GM) to supply adjustable pedal systems for Chevrolet and GMC light trucks that used engines with computer-controlled throttles. To make the '976 pedal compatible with the trucks, KSR merely took that design and added a modular sensor.

Teleflex is a rival to KSR in the design and manufacture of adjustable pedals. As noted, it is the exclusive licensee of the Engelgau patent. Engelgau filed the patent application on August 22, 2000 as a continuation of a previous application for U.S. Patent No. 6,109,241, which was filed on January 26, 1999. He has sworn he invented the patent's subject matter on February 14, 1998. The Engelgau patent discloses an adjustable electronic pedal described in the specification as a "simplified vehicle control pedal assembly that is less expensive, and which uses fewer parts and is easier to package within the vehicle." Engelgau, col. 2, lines 2-5, Supplemental App. 6. Claim 4 of the patent, at issue here, describes:

"A vehicle control pedal apparatus comprising:

a support adapted to be mounted to a vehicle structure;

an adjustable pedal assembly having a pedal arm moveable in fore and aft directions with respect to said support;

a pivot for pivotally supporting said adjustable pedal assembly with respect to said support and defining a pivot axis; and

an electronic control attached to said support for controlling a vehicle system;

said apparatus characterized by said electronic control being responsive to said pivot for providing a signal that corresponds to pedal arm position as said pedal arm pivots about said pivot *1737 axis between rest and applied positions wherein the position of said pivot remains con-

stant while said pedal arm moves in fore and aft directions with respect to said pivot." *Id.*, col. 6, lines 17-36, Supplemental App. 8 (diagram numbers omitted).

We agree with the District Court that the claim discloses "a position-adjustable pedal assembly with an electronic pedal position sensor attached to the support member of the pedal assembly. Attaching the sensor to the support member allows the sensor to remain in a fixed position while the driver adjusts the pedal." 298 F.Supp.2d, at 586-587.

Before issuing the Engelgau patent the U.S. Patent and Trademark Office (PTO) rejected one of the patent claims that was similar to, but broader than, the present claim 4. The claim did not include the requirement that the sensor be placed on a fixed pivot point. The PTO concluded the claim was an obvious combination of the prior art disclosed in Redding and Smith, explaining:

" 'Since the prior art references are from the field of endeavor, the purpose disclosed ... would have been recognized in the pertinent art of Redding. Therefore it would have been obvious ... to provide the device of Redding with the ... means attached to a support member as taught by Smith.' " *Id.*, at 595.

In other words Redding provided an example of an adjustable pedal and Smith explained how to mount a sensor on a pedal's support structure, and the rejected patent claim merely put these two teachings together.

Although the broader claim was rejected, claim 4 was later allowed because it included the limitation of a fixed pivot point, which distinguished the design from Redding's. *Ibid.* Engelgau had not included Asano among the prior art references, and Asano was not mentioned in the patent's prosecution. Thus, the PTO did not have before it an adjustable pedal with a fixed pivot point. The patent issued on May 29, 2001 and was assigned to Teleflex.

Upon learning of KSR's design for GM, Teleflex sent a warning letter informing KSR that its proposal would violate the Engelgau patent. " 'Teleflex believes that any supplier of a product that combines an adjustable pedal with an electronic throttle control necessarily employs technology covered by one or more' " of Teleflex's patents. *Id.*, at 585. KSR refused to enter a royalty arrangement with Teleflex; so Teleflex sued for infringement, asserting KSR's pedal infringed the Engelgau patent and two other patents. *Ibid.* Teleflex later abandoned its claims regarding the other patents and dedicated the patents to the public. The remaining contention was that KSR's pedal system for GM infringed claim 4 of the Engelgau patent. Teleflex has not argued that the other three claims of the patent are infringed by KSR's pedal, nor has Teleflex argued that the mechanical adjustable pedal designed by KSR for Ford infringed any of its patents.

C

The District Court granted summary judgment in KSR's favor. After reviewing the pertinent history of pedal design, the scope of the Engelgau patent, and the relevant prior art, the court considered the validity of the contested claim. By direction of 35 U.S.C. § 282, an issued patent is presumed valid. The District Court applied *Graham's* framework to determine whether under summary-judgment standards KSR had overcome the presumption and demonstrated that claim 4 was obvious in light of the prior art in existence when *1738 the claimed subject matter was invented. See § 102(a).

The District Court determined, in light of the expert testimony and the parties' stipulations, that the level of ordinary skill in pedal design was " 'an undergraduate degree in mechanical engineering (or an equivalent amount of industry experience) [and] familiarity with pedal control systems for vehicles.' " 298 F.Supp.2d, at 590. The court then set forth the relevant prior art, including the patents and pedal designs described above.

Following *Graham's* direction, the court compared the teachings of the prior art to the claims of Engelgau. It found "little difference." 298 F.Supp.2d, at 590. Asano taught everything contained in claim 4 except the use of a sensor to detect the pedal's position and transmit it to the computer controlling the throttle. That additional aspect was revealed in sources such as the '068 patent and the sensors used by Chevrolet.

Under the controlling cases from the Court of Appeals for the Federal Circuit, however, the District Court was not permitted to stop there. The court was required also to apply the TSM test. The District Court held KSR had satisfied the test. It reasoned (1) the state of the industry would lead inevitably to combinations of electronic sensors and adjustable pedals, (2) Rixon provided the basis for these developments, and (3) Smith taught a solution to the wire chafing problems in Rixon, namely locating the sensor on the fixed structure of the pedal. This could lead to the combination of Asano, or a pedal like it, with a pedal position sensor.

The conclusion that the Engelgau design was obvious was supported, in the District Court's view, by the PTO's rejection of the broader version of claim 4. Had Engelgau included Asano in his patent application, it reasoned, the PTO would have found claim 4 to be an obvious combination of Asano and Smith, as it had found the broader version an obvious combination of Redding and Smith. As a final matter, the District Court held that the secondary factor of Teleflex's commercial success with pedals based on Engelgau's design did not alter its conclusion. The District Court granted summary judgment for KSR.

With principal reliance on the TSM test, the Court of Appeals reversed. It ruled the District Court had not been strict enough in applying the test, having failed to make " 'finding[s] as to the specific understanding or principle within the knowledge of a skilled artisan that would have motivated one with no knowledge of [the] invention'... to attach an electronic control to the support bracket of the As-

ano assembly.” 119 Fed.Appx., at 288 (brackets in original) (quoting *In re Kotzab*, 217 F.3d 1365, 1371 (C.A.Fed.2000)). The Court of Appeals held that the District Court was incorrect that the nature of the problem to be solved satisfied this requirement because unless the “prior art references address[ed] the precise problem that the patentee was trying to solve,” the problem would not motivate an inventor to look at those references. 119 Fed.Appx., at 288.

Here, the Court of Appeals found, the Asano pedal was designed to solve the “ ‘constant ratio problem’ ”—that is, to ensure that the force required to depress the pedal is the same no matter how the pedal is adjusted—whereas Engelgau sought to provide a simpler, smaller, cheaper adjustable electronic pedal. *Ibid.* As for Rixon, the court explained, that pedal suffered from the problem of wire chafing but was not designed to solve it. In the court's view Rixon did not teach anything helpful to Engelgau's purpose. Smith, in turn, did not relate to adjustable pedals and did not “necessarily go to the issue of motivation *1739 to attach the electronic control on the support bracket of the pedal assembly.” *Ibid.* When the patents were interpreted in this way, the Court of Appeals held, they would not have led a person of ordinary skill to put a sensor on the sort of pedal described in Asano.

That it might have been obvious to try the combination of Asano and a sensor was likewise irrelevant, in the court's view, because “ ‘ “[o]bvious to try” has long been held not to constitute obviousness.’ ” *Id.*, at 289 (quoting *In re Deuel*, 51 F.3d 1552, 1559 (C.A.Fed.1995)).

The Court of Appeals also faulted the District Court's consideration of the PTO's rejection of the broader version of claim 4. The District Court's role, the Court of Appeals explained, was not to speculate regarding what the PTO might have done had the Engelgau patent mentioned Asano. Rather, the court held, the District Court was obliged first to presume that the issued patent was valid and then to render its own independent judgment of obvious-

ness based on a review of the prior art. The fact that the PTO had rejected the broader version of claim 4, the Court of Appeals said, had no place in that analysis.

The Court of Appeals further held that genuine issues of material fact precluded summary judgment. Teleflex had proffered statements from one expert that claim 4 “ ‘was a simple, elegant, and novel combination of features,’ ” 119 Fed.Appx., at 290, compared to Rixon, and from another expert that claim 4 was nonobvious because, unlike in Rixon, the sensor was mounted on the support bracket rather than the pedal itself. This evidence, the court concluded, sufficed to require a trial.

II

A

We begin by rejecting the rigid approach of the Court of Appeals. Throughout this Court's engagement with the question of obviousness, our cases have set forth an expansive and flexible approach inconsistent with the way the Court of Appeals applied its TSM test here. To be sure, *Graham* recognized the need for “uniformity and definiteness.” 383 U.S., at 18, 86 S.Ct. 684. Yet the principles laid down in *Graham* reaffirmed the “functional approach” of *Hotchkiss*, 11 How. 248, 13 L.Ed. 683. See 383 U.S., at 12, 86 S.Ct. 684. To this end, *Graham* set forth a broad inquiry and invited courts, where appropriate, to look at any secondary considerations that would prove instructive. *Id.*, at 17, 86 S.Ct. 684.

Neither the enactment of § 103 nor the analysis in *Graham* disturbed this Court's earlier instructions concerning the need for caution in granting a patent based on the combination of elements found in the prior art. For over a half century, the Court has held that a “patent for a combination which only unites old elements with no change in their respective functions ... obviously withdraws what is already

known into the field of its monopoly and diminishes the resources available to skillful men.” *Great Atlantic & Pacific Tea Co. v. Supermarket Equipment Corp.*, 340 U.S. 147, 152, 71 S.Ct. 127, 95 L.Ed. 162 (1950). This is a principal reason for declining to allow patents for what is obvious. The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results. Three cases decided after *Graham* illustrate the application of this doctrine.

In *United States v. Adams*, 383 U.S. 39, 40, 86 S.Ct. 708, 15 L.Ed.2d 572 (1966), a companion case to *Graham*, the Court considered the obviousness of a “wet battery” that varied from prior designs in two ways: *1740 It contained water, rather than the acids conventionally employed in storage batteries; and its electrodes were magnesium and cuprous chloride, rather than zinc and silver chloride. The Court recognized that when a patent claims a structure already known in the prior art that is altered by the mere substitution of one element for another known in the field, the combination must do more than yield a predictable result. 383 U.S., at 50-51, 86 S.Ct. 708. It nevertheless rejected the Government's claim that Adams's battery was obvious. The Court relied upon the corollary principle that when the prior art teaches away from combining certain known elements, discovery of a successful means of combining them is more likely to be nonobvious. *Id.*, at 51-52, 86 S.Ct. 708. When Adams designed his battery, the prior art warned that risks were involved in using the types of electrodes he employed. The fact that the elements worked together in an unexpected and fruitful manner supported the conclusion that Adams's design was not obvious to those skilled in the art.

In *Anderson's-Black Rock, Inc. v. Pavement Salvage Co.*, 396 U.S. 57, 90 S.Ct. 305, 24 L.Ed.2d 258 (1969), the Court elaborated on this approach. The subject matter of the patent before the Court was a device combining two pre-existing elements: a radiant-heat burner and a paving machine. The

device, the Court concluded, did not create some new synergy: The radiant-heat burner functioned just as a burner was expected to function; and the paving machine did the same. The two in combination did no more than they would in separate, sequential operation. *Id.*, at 60-62, 90 S.Ct. 305. In those circumstances, “while the combination of old elements performed a useful function, it added nothing to the nature and quality of the radiant-heat burner already patented,” and the patent failed under § 103. *Id.*, at 62, 90 S.Ct. 305 (footnote omitted).

Finally, in *Sakraida v. Ag Pro, Inc.*, 425 U.S. 273, 96 S.Ct. 1532, 47 L.Ed.2d 784 (1976), the Court derived from the precedents the conclusion that when a patent “simply arranges old elements with each performing the same function it had been known to perform” and yields no more than one would expect from such an arrangement, the combination is obvious. *Id.*, at 282, 96 S.Ct. 1532.

[1] The principles underlying these cases are instructive when the question is whether a patent claiming the combination of elements of prior art is obvious. When a work is available in one field of endeavor, design incentives and other market forces can prompt variations of it, either in the same field or a different one. If a person of ordinary skill can implement a predictable variation, § 103 likely bars its patentability. For the same reason, if a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill. *Sakraida* and *Anderson's-Black Rock* are illustrative—a court must ask whether the improvement is more than the predictable use of prior art elements according to their established functions.

Following these principles may be more difficult in other cases than it is here because the claimed subject matter may involve more than the simple substitution of one known element for another or the mere application of a known technique to a piece of

prior art ready for the improvement. Often, it will be necessary for a court to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having *1741 ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue. To facilitate review, this analysis should be made explicit. See *In re Kahn*, 441 F.3d 977, 988 (C.A.Fed.2006) (“[R]jections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness”). As our precedents make clear, however, the analysis need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ.

B

[2] When it first established the requirement of demonstrating a teaching, suggestion, or motivation to combine known elements in order to show that the combination is obvious, the Court of Customs and Patent Appeals captured a helpful insight. See *Application of Bergel*, 48 C.C.P.A. 1102, 292 F.2d 955, 956-957 (1961). As is clear from cases such as *Adams*, a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art. Although common sense directs one to look with care at a patent application that claims as innovation the combination of two known devices according to their established functions, it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does. This is so because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed

discoveries almost of necessity will be combinations of what, in some sense, is already known.

Helpful insights, however, need not become rigid and mandatory formulas; and when it is so applied, the TSM test is incompatible with our precedents. The obviousness analysis cannot be confined by a formalistic conception of the words teaching, suggestion, and motivation, or by overemphasis on the importance of published articles and the explicit content of issued patents. The diversity of inventive pursuits and of modern technology counsels against limiting the analysis in this way. In many fields it may be that there is little discussion of obvious techniques or combinations, and it often may be the case that market demand, rather than scientific literature, will drive design trends. Granting patent protection to advances that would occur in the ordinary course without real innovation retards progress and may, in the case of patents combining previously known elements, deprive prior inventions of their value or utility.

In the years since the Court of Customs and Patent Appeals set forth the essence of the TSM test, the Court of Appeals no doubt has applied the test in accord with these principles in many cases. There is no necessary inconsistency between the idea underlying the TSM test and the *Graham* analysis. But when a court transforms the general principle into a rigid rule that limits the obviousness inquiry, as the Court of Appeals did here, it errs.

C

[3][4] The flaws in the analysis of the Court of Appeals relate for the most part to the court's narrow conception of the obviousness inquiry reflected in its application of the TSM test. In determining whether the subject matter of a patent claim is obvious, neither the particular motivation nor the avowed purpose of the *1742 patentee controls. What matters is the objective reach of the claim. If the claim extends to what is obvious, it is invalid under § 103. One of the ways in which a patent's

subject matter can be proved obvious is by noting that there existed at the time of invention a known problem for which there was an obvious solution encompassed by the patent's claims.

[5] The first error of the Court of Appeals in this case was to foreclose this reasoning by holding that courts and patent examiners should look only to the problem the patentee was trying to solve. 119 Fed.Appx., at 288. The Court of Appeals failed to recognize that the problem motivating the patentee may be only one of many addressed by the patent's subject matter. The question is not whether the combination was obvious to the patentee but whether the combination was obvious to a person with ordinary skill in the art. Under the correct analysis, any need or problem known in the field of endeavor at the time of invention and addressed by the patent can provide a reason for combining the elements in the manner claimed.

The second error of the Court of Appeals lay in its assumption that a person of ordinary skill attempting to solve a problem will be led only to those elements of prior art designed to solve the same problem. *Ibid.* The primary purpose of Asano was solving the constant ratio problem; so, the court concluded, an inventor considering how to put a sensor on an adjustable pedal would have no reason to consider putting it on the Asano pedal. *Ibid.* Common sense teaches, however, that familiar items may have obvious uses beyond their primary purposes, and in many cases a person of ordinary skill will be able to fit the teachings of multiple patents together like pieces of a puzzle. Regardless of Asano's primary purpose, the design provided an obvious example of an adjustable pedal with a fixed pivot point; and the prior art was replete with patents indicating that a fixed pivot point was an ideal mount for a sensor. The idea that a designer hoping to make an adjustable electronic pedal would ignore Asano because Asano was designed to solve the constant ratio problem makes little sense. A person of ordinary skill is also a person of ordinary creativity, not an automaton.

[6] The same constricted analysis led the Court of Appeals to conclude, in error, that a patent claim cannot be proved obvious merely by showing that the combination of elements was "obvious to try." *Id.*, at 289 (internal quotation marks omitted). When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103.

The Court of Appeals, finally, drew the wrong conclusion from the risk of courts and patent examiners falling prey to hindsight bias. A factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon *ex post* reasoning. See *Graham*, 383 U.S., at 36, 86 S.Ct. 684 (warning against a "temptation to read into the prior art the teachings of the invention in issue" and instructing courts to "guard against slipping into the use of hindsight" (quoting *Monroe Auto Equipment Co. v. Heckethorn Mfg. & Supply Co.*, 332 F.2d 406, 412 (C.A.6 1964))). Rigid preventative rules that deny factfinders recourse to common sense, however, are *1743 neither necessary under our case law nor consistent with it.

We note the Court of Appeals has since elaborated a broader conception of the TSM test than was applied in the instant matter. See, e.g., *DyStar Textilfarben GmbH & Co. Deutschland KG v. C.H. Patrick Co.*, 464 F.3d 1356, 1367 (2006) ("Our suggestion test is in actuality quite flexible and not only permits, but *requires*, consideration of common knowledge and common sense"); *Alza Corp. v. Mylan Labs., Inc.*, 464 F.3d 1286, 1291 (2006) ("There is flexibility in our obviousness jurisprudence because a motivation may be found *implicitly* in the prior art. We do not have a rigid test that re-

quires an actual teaching to combine ..."). Those decisions, of course, are not now before us and do not correct the errors of law made by the Court of Appeals in this case. The extent to which they may describe an analysis more consistent with our earlier precedents and our decision here is a matter for the Court of Appeals to consider in its future cases. What we hold is that the fundamental misunderstandings identified above led the Court of Appeals in this case to apply a test inconsistent with our patent law decisions.

III

[7] When we apply the standards we have explained to the instant facts, claim 4 must be found obvious. We agree with and adopt the District Court's recitation of the relevant prior art and its determination of the level of ordinary skill in the field. As did the District Court, we see little difference between the teachings of Asano and Smith and the adjustable electronic pedal disclosed in claim 4 of the Engelgau patent. A person having ordinary skill in the art could have combined Asano with a pedal position sensor in a fashion encompassed by claim 4, and would have seen the benefits of doing so.

A

Teleflex argues in passing that the Asano pedal cannot be combined with a sensor in the manner described by claim 4 because of the design of Asano's pivot mechanisms. See Brief for Respondents 48-49, and n. 17. Therefore, Teleflex reasons, even if adding a sensor to Asano was obvious, that does not establish that claim 4 encompasses obvious subject matter. This argument was not, however, raised before the District Court. There Teleflex was content to assert only that the problem motivating the invention claimed by the Engelgau patent would not lead to the solution of combining of Asano with a sensor. See Teleflex's Response to KSR's Motion for Summary Judgment of Invalidity in No. 02-74586 (ED Mich.), pp. 18-20, App. 144a-146a.

It is also unclear whether the current argument was raised before the Court of Appeals, where Teleflex advanced the nonspecific, conclusory contention that combining Asano with a sensor would not satisfy the limitations of claim 4. See Brief for Plaintiffs-Appellants in No. 04-1152 (CA Fed.), pp. 42-44. Teleflex's own expert declarations, moreover, do not support the point Teleflex now raises. See Declaration of Clark J. Radcliffe, Ph.D., Supplemental App. 204-207; Declaration of Timothy L. Andresen, *id.*, at 208-210. The only statement in either declaration that might bear on the argument is found in the Radcliffe declaration:

"Asano ... and Rixon ... are complex mechanical linkage-based devices that are expensive to produce and assemble and difficult to package. It is exactly these difficulties with prior art designs that [Engelgau] resolves. The use of an adjustable pedal with a single pivot reflecting pedal position combined with an electronic control mounted between the *1744 support and the adjustment assembly at that pivot was a simple, elegant, and novel combination of features in the Engelgau '565 patent." *Id.*, at 206, ¶ 16.

Read in the context of the declaration as a whole, this is best interpreted to mean that Asano could not be used to solve "[t]he problem addressed by Engelgau '565[:] to provide a less expensive, more quickly assembled, and smaller package adjustable pedal assembly with electronic control." *Id.*, at 205, ¶ 10.

The District Court found that combining Asano with a pivot-mounted pedal position sensor fell within the scope of claim 4. 298 F.Supp.2d, at 592-593. Given the significance of that finding to the District Court's judgment, it is apparent that Teleflex would have made clearer challenges to it if it intended to preserve this claim. In light of Teleflex's failure to raise the argument in a clear fashion, and the silence of the Court of Appeals on the issue, we take the District Court's conclusion on the point to be correct.

B

The District Court was correct to conclude that, as of the time Engelgau designed the subject matter in claim 4, it was obvious to a person of ordinary skill to combine Asano with a pivot-mounted pedal position sensor. There then existed a marketplace that created a strong incentive to convert mechanical pedals to electronic pedals, and the prior art taught a number of methods for achieving this advance. The Court of Appeals considered the issue too narrowly by, in effect, asking whether a pedal designer writing on a blank slate would have chosen both Asano and a modular sensor similar to the ones used in the Chevrolet truckline and disclosed in the '068 patent. The District Court employed this narrow inquiry as well, though it reached the correct result nevertheless. The proper question to have asked was whether a pedal designer of ordinary skill, facing the wide range of needs created by developments in the field of endeavor, would have seen a benefit to upgrading Asano with a sensor.

In automotive design, as in many other fields, the interaction of multiple components means that changing one component often requires the others to be modified as well. Technological developments made it clear that engines using computer-controlled throttles would become standard. As a result, designers might have decided to design new pedals from scratch; but they also would have had reason to make pre-existing pedals work with the new engines. Indeed, upgrading its own pre-existing model led KSR to design the pedal now accused of infringing the Engelgau patent.

For a designer starting with Asano, the question was where to attach the sensor. The consequent legal question, then, is whether a pedal designer of ordinary skill starting with Asano would have found it obvious to put the sensor on a fixed pivot point. The prior art discussed above leads us to the conclusion that attaching the sensor where both KSR and Engelgau put it would have been obvious to a person of ordinary skill.

The '936 patent taught the utility of putting the sensor on the pedal device, not in the engine. Smith, in turn, explained to put the sensor not on the pedal's footpad but instead on its support structure. And from the known wire-chafing problems of Rixon, and Smith's teaching that "the pedal assemblies must not precipitate any motion in the connecting wires," Smith, col. 1, lines 35-37, Supplemental App. 274, the designer would know to place the sensor on a nonmoving part of the pedal structure. The most obvious nonmoving point on the structure from which a sensor can *1745 easily detect the pedal's position is a pivot point. The designer, accordingly, would follow Smith in mounting the sensor on a pivot, thereby designing an adjustable electronic pedal covered by claim 4.

Just as it was possible to begin with the objective to upgrade Asano to work with a computer-controlled throttle, so too was it possible to take an adjustable electronic pedal like Rixon and seek an improvement that would avoid the wire-chafing problem. Following similar steps to those just explained, a designer would learn from Smith to avoid sensor movement and would come, thereby, to Asano because Asano disclosed an adjustable pedal with a fixed pivot.

Teleflex indirectly argues that the prior art taught away from attaching a sensor to Asano because Asano in its view is bulky, complex, and expensive. The only evidence Teleflex marshals in support of this argument, however, is the Radcliffe declaration, which merely indicates that Asano would not have solved Engelgau's goal of making a small, simple, and inexpensive pedal. What the declaration does not indicate is that Asano was somehow so flawed that there was no reason to upgrade it, or pedals like it, to be compatible with modern engines. Indeed, Teleflex's own declarations refute this conclusion. Dr. Radcliffe states that Rixon suffered from the same bulk and complexity as did Asano. See *id.* at 206. Teleflex's other expert, however, explained that Rixon was itself designed by adding a sensor to a pre-existing mechanical

pedal. See *id.*, at 209. If Rixon's base pedal was not too flawed to upgrade, then Dr. Radcliffe's declaration does not show Asano was either. Teleflex may have made a plausible argument that Asano is inefficient as compared to Engelgau's preferred embodiment, but to judge Asano against Engelgau would be to engage in the very hindsight bias Teleflex rightly urges must be avoided. Accordingly, Teleflex has not shown anything in the prior art that taught away from the use of Asano.

Like the District Court, finally, we conclude Teleflex has shown no secondary factors to dislodge the determination that claim 4 is obvious. Proper application of *Graham* and our other precedents to these facts therefore leads to the conclusion that claim 4 encompassed obvious subject matter. As a result, the claim fails to meet the requirement of § 103.

We need not reach the question whether the failure to disclose Asano during the prosecution of Engelgau voids the presumption of validity given to issued patents, for claim 4 is obvious despite the presumption. We nevertheless think it appropriate to note that the rationale underlying the presumption—that the PTO, in its expertise, has approved the claim—seems much diminished here.

IV

[8] A separate ground the Court of Appeals gave for reversing the order for summary judgment was the existence of a dispute over an issue of material fact. We disagree with the Court of Appeals on this point as well. To the extent the court understood the *Graham* approach to exclude the possibility of summary judgment when an expert provides a conclusory affidavit addressing the question of obviousness, it misunderstood the role expert testimony plays in the analysis. In considering summary judgment on that question the district court can and should take into account expert testimony, which may resolve or keep open certain questions of fact. That is not the end of the issue, however. The ulti-

mate judgment of obviousness is a legal determination. *Graham*, 383 U.S., at 17, 86 S.Ct. 684. Where, as here, the content of the prior art, the scope of the patent *1746 claim, and the level of ordinary skill in the art are not in material dispute, and the obviousness of the claim is apparent in light of these factors, summary judgment is appropriate. Nothing in the declarations proffered by Teleflex prevented the District Court from reaching the careful conclusions underlying its order for summary judgment in this case.

* * *

We build and create by bringing to the tangible and palpable reality around us new works based on instinct, simple logic, ordinary inferences, extraordinary ideas, and sometimes even genius. These advances, once part of our shared knowledge, define a new threshold from which innovation starts once more. And as progress beginning from higher levels of achievement is expected in the normal course, the results of ordinary innovation are not the subject of exclusive rights under the patent laws. Were it otherwise patents might stifle, rather than promote, the progress of useful arts. See U.S. Const., Art. I, § 8, cl. 8. These premises led to the bar on patents claiming obvious subject matter established in *Hotchkiss* and codified in § 103. Application of the bar must not be confined within a test or formulation too constrained to serve its purpose.

KSR provided convincing evidence that mounting a modular sensor on a fixed pivot point of the Asano pedal was a design step well within the grasp of a person of ordinary skill in the relevant art. Its arguments, and the record, demonstrate that claim 4 of the Engelgau patent is obvious. In rejecting the District Court's rulings, the Court of Appeals analyzed the issue in a narrow, rigid manner inconsistent with § 103 and our precedents. The judgment of the Court of Appeals is reversed, and the case remanded for further proceedings consistent with this opinion.

127 S.Ct. 1727, 167 L.Ed.2d 705, 75 USLW 4289, 82 U.S.P.Q.2d 1385, 07 Cal. Daily Op. Serv. 4654, 20 Fla. L. Weekly Fed. S 248

(Cite as: 127 S.Ct. 1727)

It is so ordered.

U.S.,2007.

KSR Intern. Co. v. Teleflex Inc.

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ence was before the examiner, whether through the examiner's search or the applicant's disclosure, it can not be deemed to have been withheld from the examiner.").

Because the district court clearly erred in determining that the statements in the October 2005 Response were affirmative misrepresentations of material fact and because there was no failure to disclose information while the reexamination was still pending before the PTO, we conclude that the district court erred in granting summary judgment of inequitable conduct.

CONCLUSION

Because we conclude that the term "near" is not indefinite, we reverse the district court's grant of judgment of invalidity for indefiniteness. Because we determine that no affirmative misrepresentation of material fact occurred and that there was not a failure to timely disclose material information, we reverse the summary judgment of unenforceability.

REVERSED



TAKEDA CHEMICAL INDUSTRIES, LTD. and Takeda Pharmaceuticals North America, INC., Plaintiffs-Appellees,

v.

ALPHAPHARM PTY., LTD. and Genpharm, Inc., Defendants-Appellants.

No. 06-1329.

United States Court of Appeals,
Federal Circuit.

June 28, 2007.

Background: Owner of patent for diabetes drug brought infringement actions

against proposed manufacturers of generic versions. The United States District Court for the Southern District of New York, Denise Cote, J., 417 F.Supp.2d 341, granted judgment for owner. Manufacturers appealed.

Holdings: The Court of Appeals, Lourie, Circuit Judge, held that:

- (1) person of ordinary skill in the art would not have selected closest prior art compound as lead compound for antidiabetic treatment;
- (2) person of ordinary skill in the art would not have been prompted to modify closest prior art compound, using steps of homologation or ring-walking, to synthesize claimed compound; and
- (3) any error was harmless that district court may have committed by incorrectly implying that prosecution histories were not accessible to public.

Affirmed.

Dyk, Circuit Judge, filed concurring opinion.

1. Patents \S 16.25

Person of ordinary skill in the art would not have selected closest prior art compound as lead compound for antidiabetic treatment, and thus presumption of motivation did not apply on competitor's claim of obviousness; although prosecution history of patent included statement characterizing compound as "especially important," any suggestion to select compound was essentially negated given more exhaustive and reliable scientific analysis which taught away from compound and evidence from similar contemporaneously filed patents showed that there were many promising, broad avenues for further research. 35 U.S.C.A. \S 103.

2. Patents \S 312(4)

Because a patent is presumed to be valid, the evidentiary burden to show facts supporting a conclusion of invalidity, which rests on the accused infringer, is one of clear and convincing evidence. 35 U.S.C.A. \S 282.

3. Patents \S 324.5, 324.55(4)

Whether an invention would have been obvious is a question of law, reviewed de novo, based upon underlying factual questions which are reviewed for clear error following a bench trial. 35 U.S.C.A. \S 103.

4. Patents \S 16(2, 3), 36.1(1)

The factors that control an obviousness inquiry are: (1) the scope and content of the prior art; (2) the differences between the prior art and the claims; (3) the level of ordinary skill in the pertinent art; and (4) objective evidence of nonobviousness. 35 U.S.C.A. \S 103.

5. Patents \S 16.25

In a case involving a patent on a new chemical compound, some reason must be identified that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound. 35 U.S.C.A. \S 103.

6. Patents \S 16.25

Person of ordinary skill in the art would not have been prompted to modify closest prior art compound, using steps of homologation or ring-walking, to synthesize claimed compound in patent for antidiabetic treatment, and thus claimed compound was not obvious, where process of modifying lead compounds was not routine at time of invention, nothing in prior art

provided reasonable expectation that adding methyl group to compound would have reduced or eliminated toxicity of lead compound, there was no reasonable expectation in the art that changing positions of substituent on pyridyl ring would have resulted in beneficial changes, and claimed compound differed significantly from lead compound, of which it was not a homolog, in terms of toxicity. 35 U.S.C.A. \S 103.

7. Patents \S 168(2.1)

Statement made during prosecution of patent for antidiabetic treatment in response to enablement rejection, indicating only that changes to left moiety of lead compound would create compounds with same properties as compounds of prior art, did not represent that lower toxicity would result from change, for purpose of obviousness claim. 35 U.S.C.A. \S 103.

8. Patents \S 324.56

Any error was harmless that district court may have committed by incorrectly implying that prosecution histories were not accessible to public, on competitor's claim of obviousness, where court nonetheless considered prosecution history of patent in its obviousness analysis and accorded proper weight to statements contained therein. 35 U.S.C.A. \S 103.

Patents \S 328(2)

4,287,200. Cited as Prior Art.

Patents \S 328(2)

4,340,605, 4,438,141, 4,444,779. Cited.

Patents \S 328(2)

4,687,777. Valid.

David G. Conlin, Edwards Angell Palmer & Dodge LLP, of Boston, MA, argued

for plaintiffs-appellees. With him on the brief were Barbara L. Moore, Kathleen B. Carr, and Adam P. Samansky; and Anthony J. Viola and Andre K. Cizmarik, of New York, NY. Of counsel on the brief was Mark Chao, Takeda Pharmaceuticals North America, Inc., of Lincolnshire, IL.

Kevin F. Murphy, Frommer Lawrence & Haug LLP, of New York, NY, argued for defendants-appellants. With him on the brief were Edgar H. Haug and Jeffrey A. Hovden.

Before LOURIE, BRYSON, and DYK, Circuit Judges.

Opinion for the court filed by Circuit Judge LOURIE. Concurring opinion filed by Circuit Judge DYK.

LOURIE, Circuit Judge.

Alphapharm Pty., Ltd. and Genpharm, Inc. (collectively “Alphapharm”) appeal from the decision of the United States District Court for the Southern District of New York, following a bench trial, that U.S. Patent 4,687,777 was not shown to be invalid under 35 U.S.C. § 103. *Takeda Chem. Indus., Ltd. v. Mylan Labs.*, 417 F.Supp.2d 341 (S.D.N.Y.2006). Because we conclude that the district court did not err in determining that the claimed compounds would not have been obvious in light of the prior art, and hence that the patent has not been shown to be invalid, we affirm.

BACKGROUND

Diabetes is a disease that is characterized by the body’s inability to regulate blood sugar. It is generally caused by inadequate levels of insulin—a hormone produced in the pancreas. Insulin allows

blood sugar or glucose, which is derived from food, to enter into the body’s cells and be converted into energy. There are two types of diabetes, known as Type 1 and Type 2. In Type 1 diabetes, the pancreas fails to produce insulin, and individuals suffering from this type of diabetes must regularly receive insulin from an external source. In contrast, Type 2 diabetic individuals produce insulin. However, their bodies are unable to effectively use the insulin that is produced. This is also referred to as insulin resistance. As a result, glucose is unable to enter the cells, thereby depriving the body of its main source of energy. Type 2 diabetes is the most common form of diabetes—affecting over 90% of diabetic individuals.

In the 1990s, a class of drugs known as thiazolidinediones (“TZDs”) was introduced on the market as a treatment for Type 2 diabetes. Takeda Chemical Industries, Ltd., and Takeda Pharmaceuticals North America, Inc. (collectively “Takeda”) first invented certain TZDs in the 1970s. Takeda’s research revealed that TZDs acted as insulin sensitizers, *i.e.*, compounds that ameliorate insulin resistance. Although the function of TZDs was not completely understood, TZDs appeared to lower blood glucose levels by binding to a molecule in the nucleus of the cell known as PPARgamma, which activates insulin receptors and stimulates the production of glucose transporters. *Takeda*, 417 F.Supp.2d at 348–49. The transporters then travel to the cellular surface and enable glucose to enter the cell from the bloodstream. *Id.*

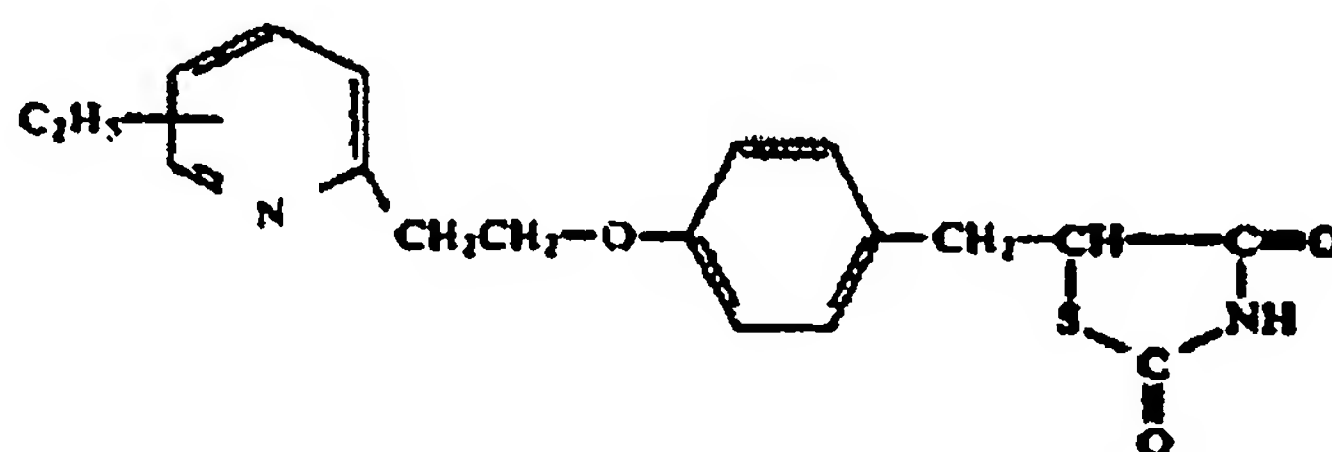
Takeda developed the drug ACTOS®, which is used to control blood sugar in patients who suffer from Type 2 diabetes. ACTOS® has enjoyed substantial commercial success since its launch in 1999. By

2003, it held 47% of the TZD market, and gross sales for that year exceeded \$1.7 billion. *Id.* at 386. The active ingredient in ACTOS® is the TZD compound pioglitazone, a compound claimed in the patent in suit.

Takeda owns U.S. Patent 4,687,777 (the “777 patent”) entitled “Thiazolidinedione Derivatives, Useful As Antidiabetic Agents.” The patent is directed to “com-

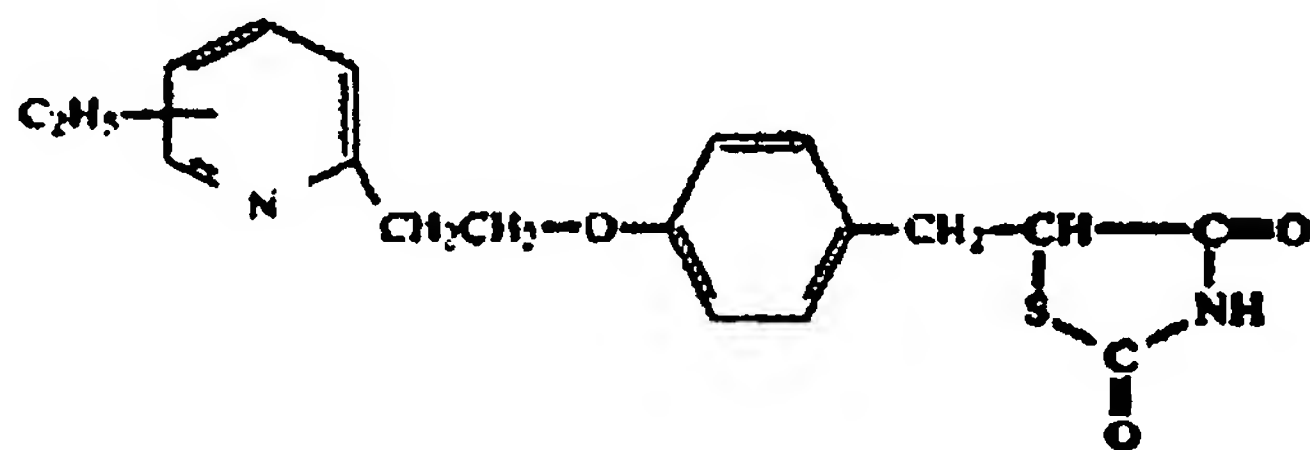
pounds which can be practically used as antidiabetic agents having a broad safety margin between pharmacological effect and toxicity or unfavorable side reactions.” ’777 patent col.1 ll.34–37. The asserted claims are claims 1, 2, and 5. Claim 1 claims a genus of compounds. Claim 5 claims pharmaceutical compositions containing that genus of compounds. Those claims read as follows:

1. A compound of the formula:



or a pharmacologically acceptable salt thereof.

5. An antidiabetic composition which consists essentially of a compound of the formula:



or a pharmacologically acceptable salt thereof, in association with a pharmacologically acceptable carrier, excipient or diluent.

Id., claims 1 & 5.

For purposes of this appeal, the critical portion of the compound structure is the left moiety of the molecule, namely, the ethyl-substituted pyridyl ring.¹ That chemical structure, which has an ethyl sub-

stituent (C² H⁵) pictorially drawn to the center of the pyridyl ring, indicates that the structure covers four possible compounds, *viz.*, compounds with an ethyl substituent located at the four available positions on the pyridyl ring. *Takeda*, 417 F.Supp.2d at 360. The formula includes the 3-ethyl compound, 4-ethyl compound, 5-ethyl compound (pioglitazone), and 6-ethyl compound.

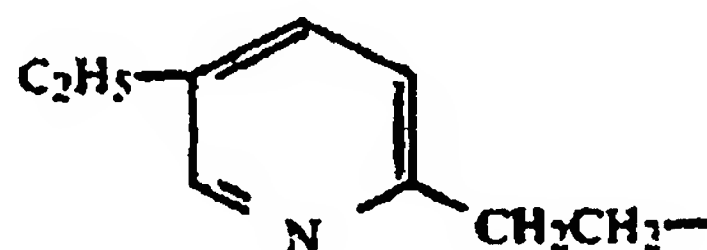
1. Pyridine is a “six-membered carbon-containing ring with one carbon replaced by a

nitrogen.” *Takeda*, 417 F.Supp.2d at 351.

Claim 2 of the '777 patent covers the single compound pioglitazone. That claim, which depends from claim 1, reads:

2. A compound as claimed in claim 1, wherein the compound is 5-{4-[2-(5-ethyl-2-pyridyl)ethoxy] benzyl}-2,4-thiazolidinedione.

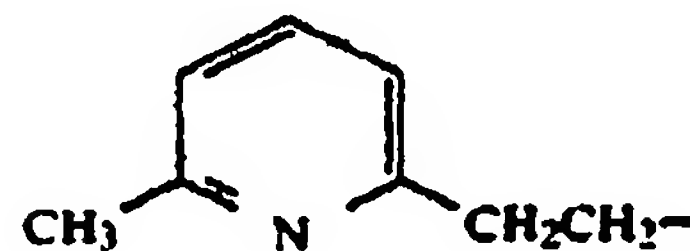
'777 patent, claim 2. Pioglitazone is referred to as the 5-ethyl compound because the ethyl substituent is attached to the 5-position on the pyridyl ring. That portion of the compound is depicted as:



Alphapharm, a generic drug manufacturer, filed an Abbreviated New Drug Application ("ANDA") pursuant to the Hatch-Waxman Act seeking U.S. Food and Drug Administration ("FDA") approval under 21 U.S.C. § 355(j) et seq. to manufacture and sell a generic version of pioglitazone. Alphapharm filed a Paragraph IV certification with its ANDA pursuant to § 505(j)(2)(B)(ii), asserting that the '777 patent is invalid as obvious under 35 U.S.C. § 103. In response, Takeda sued Alphapharm, along with three other generic drug manufacturers who also sought FDA approval to market generic pioglitazone, alleging that the defendants have infringed or will infringe the '777 patent.

On January 17, 2006, the district court commenced a bench trial solely on the issues of validity and enforceability of the '777 patent. Alphapharm advanced its invalidity argument, asserting that the claimed compounds would have been obvious at the time of the alleged invention. Alphapharm's obviousness contention rested entirely on a prior art TZD compound

that is referenced in Table 1 of the '777 patent as compound b. The left moiety of compound b consists of a pyridyl ring with a methyl (CH³) group attached to the 6-position of the ring. That portion of its chemical structure is illustrated as follows:



Alphapharm asserted that the claimed compounds would have been obvious over compound b.

The district court found that Alphapharm failed to prove by clear and convincing evidence that the asserted claims were invalid as obvious under 35 U.S.C. § 103. The court first concluded that there was no motivation in the prior art to select compound b as the lead compound for antidiabetic research, and that the prior art taught away from its use. As such, the court concluded that Alphapharm failed to make a prima facie case of obviousness. The court continued its analysis and found that even if Alphapharm succeeded in making a prima facie showing, Takeda would still prevail because any prima facie case of obviousness was rebutted by the unexpected results of pioglitazone's non-toxicity. The court then rendered judgment in favor of Takeda. The district court also held that the '777 patent had not been procured through inequitable conduct. That decision has been separately appealed and has been affirmed in a decision issued today.

Alphapharm timely appealed. We have jurisdiction pursuant to 28 U.S.C. § 1295(a)(1).

DISCUSSION

A. *Standard of Review*

[1-3] In this appeal, we are presented with one issue, namely, whether the as-

serted claims of the '777 patent would have been obvious under 35 U.S.C. § 103 at the time the invention was made. An invention is not patentable, *inter alia*, "if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art." 35 U.S.C. § 103(a). Because a patent is presumed to be valid, 35 U.S.C. § 282, the evidentiary burden to show facts supporting a conclusion of invalidity, which rests on the accused infringer, is one of clear and convincing evidence. *AK Steel Corp. v. Sollac & Ugine*, 344 F.3d 1234, 1238–39 (Fed.Cir. 2003). Whether an invention would have been obvious under 35 U.S.C. § 103 is a "question of law, reviewed de novo, based upon underlying factual questions which are reviewed for clear error following a bench trial." *Alza Corp. v. Mylan Labs., Inc.*, 464 F.3d 1286, 1289 (Fed.Cir.2006).

B. Obviousness

Alphapharm raises three main arguments in support of its contention that the claims would have been obvious. First, Alphapharm asserts that the district court misapplied the law, particularly the law governing obviousness in the context of structurally similar chemical compounds. According to Alphapharm, the record established that compound b was the most effective antidiabetic compound in the prior art, and thus the court erred by failing to apply a presumption that one of ordinary skill in the art would have been motivated to make the claimed compounds. Alphapharm asserts that such a conclusion is mandated by our case law, including our en banc decision in *In re Dillon*, 919 F.2d 688 (Fed.Cir.1990). Second, Alphapharm argues that the court erred in determining

the scope and content of the prior art, in particular, whether to include the prosecution history of the prior '779 patent. Lastly, Alphapharm assigns error to numerous legal and factual determinations and certain evidentiary rulings that the court made during the course of the trial.

Takeda responds that the district court correctly determined that Alphapharm failed to prove by clear and convincing evidence that the asserted claims are invalid as obvious. Takeda contends that there was overwhelming evidence presented at trial to support the court's conclusion that no motivation existed in the prior art for one of ordinary skill in the art to select compound b as a lead compound, and even if there was, that the unexpected results of pioglitazone's improved toxicity would have rebutted any prima facie showing of obviousness. Takeda further argues that all of Alphapharm's remaining challenges to the district court's legal and factual rulings are simply without merit.

[4] We agree with Takeda that the district court did not err in concluding that the asserted claims of the '777 patent would not have been obvious. The Supreme Court recently addressed the issue of obviousness in *KSR International Co. v. Teleflex Inc.*, — U.S. —, 127 S.Ct. 1727, 167 L.Ed.2d 705 (2007). The Court stated that the *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 86 S.Ct. 684, 15 L.Ed.2d 545 (1966), factors still control an obviousness inquiry. Those factors are: 1) "the scope and content of the prior art"; 2) the "differences between the prior art and the claims"; 3) "the level of ordinary skill in the pertinent art"; and 4) objective evidence of nonobviousness. *KSR*, 127 S.Ct. at 1734 (quoting *Graham*, 383 U.S. at 17–18, 86 S.Ct. 684).

In a thorough and well-reasoned opinion, albeit rendered before *KSR* was decided

by the Supreme Court, the district court made extensive findings of fact and conclusions of law as to the four *Graham* factors. Alphapharm's arguments challenge the court's determinations with respect to certain of these factors, which we now address.

1. *Differences Between the Prior Art and the Claims*

a. *Selection of Compound b as Lead Compound*

Alphapharm's first argument challenges the court's determination with regard to the "differences between the prior art and the claims." Alphapharm contends that the court erred as a matter of law in holding that the ethyl-substituted TZDs were nonobvious in light of the closest prior art compound, compound b, by misapplying the law relating to obviousness of chemical compounds.

We disagree. Our case law concerning prima facie obviousness of structurally similar compounds is well-established. We have held that "structural similarity between claimed and prior art subject matter, proved by combining references or otherwise, where the prior art gives reason or motivation to make the claimed compositions, creates a prima facie case of obviousness." *Dillon*, 919 F.2d at 692. In addition to structural similarity between the compounds, a prima facie case of obviousness also requires a showing of "adequate support in the prior art" for the change in structure. *In re Grabiak*, 769 F.2d 729, 731-32 (Fed.Cir.1985).

2. We note that the Supreme Court in its *KSR* opinion referred to the issue as whether claimed subject matter "was" or "was not" obvious. Since 35 U.S.C. § 103 uses the language "would have been obvious," and the Supreme Court in *KSR* did consider the particular time at which obviousness is deter-

We elaborated on this requirement in the case of *In re Deuel*, 51 F.3d 1552, 1558 (Fed.Cir.1995), where we stated that "[n]ormally a prima facie case of obviousness is based upon structural similarity, i.e., an established structural relationship between a prior art compound and the claimed compound." That is so because close or established "[s]tructural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds." *Id.* A known compound may suggest its homolog, analog, or isomer because such compounds "often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties." *Id.* We clarified, however, that in order to find a prima facie case of unpatentability in such instances, a showing that the "prior art would have suggested making the specific molecular modifications necessary to achieve the claimed invention" was also required. *Id.* (citing *In re Jones*, 958 F.2d 347 (Fed.Cir.1992); *Dillon*, 919 F.2d 688; *Grabiak*, 769 F.2d 729; *In re Lahu*, 747 F.2d 703 (Fed.Cir.1984)).

[5] That test for prima facie obviousness for chemical compounds is consistent with the legal principles enunciated in *KSR*.² While the *KSR* Court rejected a rigid application of the teaching, suggestion, or motivation ("TSM") test in an obviousness inquiry, the Court acknowledged the importance of identifying "a reason that would have prompted a person of ordinary skill in the relevant field to com-

mined, we consider that the Court did not in *KSR* reject the standard statutory formulation of the inquiry whether the claimed subject matter "would have been obvious at the time the invention was made." 35 U.S.C. § 103. Hence, we will continue to use the statutory "would have been" language.

bine the elements in the way the claimed new invention does" in an obviousness determination. *KSR*, 127 S.Ct. at 1731. Moreover, the Court indicated that there is "no necessary inconsistency between the idea underlying the TSM test and the *Graham* analysis." *Id.* As long as the test is not applied as a "rigid and mandatory" formula, that test can provide "helpful insight" to an obviousness inquiry. *Id.* Thus, in cases involving new chemical compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish *prima facie* obviousness of a new claimed compound.

We agree with Takeda and the district court that Alphapharm failed to make that showing here. Alphapharm argues that the prior art would have led one of ordinary skill in the art to select compound b as a lead compound. By "lead compound," we understand Alphapharm to refer to a compound in the prior art that would be most promising to modify in order to improve upon its antidiabetic activity and obtain a compound with better activity.³ Upon selecting that compound for antidiabetic research, Alphapharm asserts that one of ordinary skill in the art would have made two obvious chemical changes: first, homologation, *i.e.*, replacing the methyl group with an ethyl group, which would have resulted in a 6-ethyl compound; and second, "ring-walking," or moving the ethyl substituent to another position on the ring, the 5-position, thereby leading to the

discovery of pioglitazone. Thus, Alphapharm's obviousness argument clearly depends on a preliminary finding that one of ordinary skill in the art would have selected compound b as a lead compound.

The district court found, however, that one of ordinary skill in the art would not have selected compound b as the lead compound. In reaching its determination, the court first considered Takeda's U.S. Patent 4,287,200 (the "'200 patent"), which was issued on September 1, 1981, and its prosecution history. The court found that the '200 patent "discloses hundreds of millions of TZD compounds."⁴ *Takeda*, 417 F.Supp.2d at 378. The patent specifically identified fifty-four compounds, including compound b, that were synthesized according to the procedures described in the patent, but did not disclose experimental data or test results for any of those compounds. The prosecution history, however, disclosed test results for nine specific compounds, including compound b. That information was provided to the examiner in response to a rejection in order to show that the claimed compounds of the '200 patent were superior to the known compounds that were disclosed in a cited reference. The court, however, found nothing in the '200 patent, or in its file history, to suggest to one of ordinary skill in the art that those nine compounds, out of the hundreds of millions of compounds covered by the patent application, were the best performing compounds as antidiabetics, and hence targets for modification to seek improved properties. *Id.* at 375.

3. The parties do not dispute that compound b was the closest prior art compound. Thus, the legal question is whether or not the claimed subject matter would have been obvious over that compound. We will, however, use Alphapharm's terminology of "lead compound" in this opinion, deciding the appeal as it has been argued.

4. Three divisional applications derive from the '200 patent. Those applications matured into U.S. Patent 4,340,605, U.S. Patent 4,438,141, and U.S. Patent No. 4,444,779 (the "'779 Patent"). The '779 patent is of particular relevance in this appeal and is discussed below. *Takeda*, 417 F.Supp.2d at 378.

The court next considered an article that was published the following year in 1982 by T. Sodha et al. entitled "Studies on Antidiabetic Agents. II. Synthesis of 5-[4-(1-Methylcyclohexylmethoxy)-benzyl]thiazolidine-2,4-dione (ADD-3878) and Its Derivatives" ("Sodha II"). The Sodha II reference disclosed data relating to hypoglycemic activity and plasma triglyceride lowering activity for 101 TZD compounds. Those compounds did not include pioglitazone, but included compound b. Significantly, Sodha II identified three specific compounds that were deemed most favorable in terms of toxicity and activity. Notably, compound b was not identified as one of the three most favorable compounds. On the contrary, compound b, was singled out as causing "considerable increases in body weight and brown fat weight."

The court also considered Takeda's '779 patent. That patent covers a subset of compounds originally included in the '200 patent application, namely, TZD compounds "where the pyridyl or thiazolyl groups may be substituted." *Id.* at 353. The broadest claim of the '779 patent covers over one million compounds. *Id.* at 378. Compound b was specifically claimed in claim 4 of the patent. The court noted that a preliminary amendment in the prosecution history of the patent contained a statement that "the compounds in which these heterocyclic rings are substituted have become important, especially [compound b]." *Id.*

Based on the prior art as a whole, however, the court found that a person of ordinary skill in the art would not have selected compound b as a lead compound for antidiabetic treatment. Although the prosecution history of the '779 patent included the statement that characterized

compound b as "especially important," the court found that any suggestion to select compound b was essentially negated by the disclosure of the Sodha II reference. The court reasoned that one of ordinary skill in the art would not have chosen compound b, notwithstanding the statement in the '779 patent prosecution history, "given the more exhaustive and reliable scientific analysis presented by Sodha II, which taught away from compound b, and the evidence from all of the TZD patents that Takeda filed contemporaneously with the '779 [p]atent showing that there were many promising, broad avenues for further research." *Id.* at 380.

The court found that the three compounds that the Sodha II reference identified as "most favorable" and "valuable for the treatment of maturity-onset diabetes," not compound b, would have served as the best "starting point for further investigation" to a person of ordinary skill in the art. *Id.* at 376. Because diabetes is a chronic disease and thus would require long term treatment, the court reasoned that researchers would have been dissuaded from selecting a lead compound that exhibited negative effects, such as toxicity, or other adverse side effects, especially one that causes "considerable increases in body weight and brown fat weight." *Id.* at 376-77. Thus, the court determined that the prior art did not suggest to one of ordinary skill in the art that compound b would be the best candidate as the lead compound for antidiabetic research.

Admissions from Alphapharm witnesses further buttressed the court's conclusion. Dr. Rosenberg, head of Alphapharm's intellectual property department, testified as a 30(b)(6) witness on behalf of Alphapharm. In discussing Sodha II, Dr. Rosenberg admitted that there was nothing in

the article that would recommend that a person of ordinary skill in the art choose compound b over other compounds in the article that had the same efficacy rating. Dr. Rosenberg, acknowledging that compound b had the negative side effects of increased body weight and brown fat, also admitted that a compound with such side effects would “presumably not” be a suitable candidate compound for treatment of Type II diabetes. Alphapharm’s expert, Dr. Mosberg, concurred in that view at his deposition when he admitted that a medicinal chemist would find such side effects “undesirable.”

Moreover, another Alphapharm 30(b)(6) witness, Barry Spencer, testified at his deposition that in reviewing the prior art, one of ordinary skill in the art would have chosen three compounds in Sodha II as lead compounds for research, not solely compound b. In addition, Takeda’s witness, Dr. Morton, testified that at the time Sodha II was published, it was known that obesity contributed to insulin resistance and Type 2 diabetes. Thus, one of ordinary skill in the art would have concluded that Sodha II taught away from pyridyl compounds because it associated adverse side effects with compound b.

We do not accept Alphapharm’s assertion that *KSR*, as well as another case recently decided by this court, *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348 (Fed.Cir. 2007), mandates reversal. Relying on *KSR*, Alphapharm argues that the claimed compounds would have been obvious because the prior art compound fell within “the objective reach of the claim,” and the evidence demonstrated that using the techniques of homologation and ring-walking would have been “obvious to try.” Additionally, Alphapharm argues that our holding in *Pfizer*, where we found obvious

certain claims covering a particular acid-addition salt, directly supports its position.

We disagree. The *KSR* Court recognized that “[w]hen there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp.” *KSR*, 127 S.Ct. at 1732. In such circumstances, “the fact that a combination was obvious to try might show that it was obvious under § 103.” *Id.* That is not the case here. Rather than identify predictable solutions for antidiabetic treatment, the prior art disclosed a broad selection of compounds any one of which could have been selected as a lead compound for further investigation. Significantly, the closest prior art compound (compound b, the 6-methyl) exhibited negative properties that would have directed one of ordinary skill in the art away from that compound. Thus, this case fails to present the type of situation contemplated by the Court when it stated that an invention may be deemed obvious if it was “obvious to try.” The evidence showed that it was not obvious to try.

Similarly, Alphapharm’s reliance on *Pfizer* fares no better. In *Pfizer*, we held that certain claims covering the besylate salt of amlodipine would have been obvious. The prior art included a reference, referred to as the Berge reference, that disclosed a genus of pharmaceutically acceptable anions that could be used to form pharmaceutically acceptable acid addition salts, as well as other publications that disclosed the chemical characteristics of the besylate salt. *Pfizer*, 480 F.3d at 1363. Noting that our conclusion was based on the “particularized facts of this case,” we found that the prior art provided

“ample motivation to narrow the genus of 53 pharmaceutically-acceptable anions disclosed by Berge to a few, including benzene sulphonate.” *Id.* at 1363, 1367. Here, the court found nothing in the prior art to narrow the possibilities of a lead compound to compound b. In contrast, the court found that one of ordinary skill in the art would have chosen one of the many compounds disclosed in Sodha II, of which there were over ninety, that “did not disclose the existence of toxicity or side effects, and to engage in research to increase the efficacy and confirm the absence of toxicity of those compounds, rather than to choose as a starting point a compound with identified adverse effects.” Thus, *Pfizer* does not control this case.

Based on the record before us, we conclude that the district court’s fact-findings were not clearly erroneous and were supported by evidence in the record. Moreover, we reject the assertion that the court failed to correctly apply the law relating to *prima facie* obviousness of chemical compounds. Because Alphapharm’s obviousness argument rested entirely on the court making a preliminary finding that the prior art would have led to the selection of compound b as the lead compound, and Alphapharm failed to prove that assertion, the court did not commit reversible error by failing to apply a presumption of motivation. We thus conclude that the court did not err in holding that Alphapharm failed to establish a *prima facie* case of obviousness. See *Eli Lilly & Co. v. Zenith Goldline Pharms.*, 471 F.3d 1369 (Fed.Cir. 2006) (affirming the district court’s finding of nonobviousness upon concluding, in part, that the prior art compound would not have been chosen as a lead compound).

b. Choice of the Claimed Compounds

[6] Even if Alphapharm had established that preliminary finding, and we

have concluded that it did not, the record demonstrates that Alphapharm’s obviousness argument fails on a second ground. The district court found nothing in the prior art to suggest making the specific molecular modifications to compound b that are necessary to achieve the claimed compounds. In reaching that conclusion, the court first found that the process of modifying lead compounds was not routine at the time of the invention. *Takeda*, 417 F.Supp.2d at 380. Dr. Mosberg opined that the steps of homologation and ring-walking were “routine steps in the drug optimization process,” but the court found that testimony unavailing in light of the contrary, more credible, testimony offered by Takeda’s experts. *Id.* at 381. In addition, the court relied on Dr. Rosenberg’s admission that a person of ordinary skill in the art would “look at a host of substituents, such as chlorides, halides and others, not just methyls” in modifying the pyridyl ring. *Id.*

Pioglitazone differs from compound b in two respects, and one would have to both homologate the methyl group of compound b and move the resulting ethyl group to the 5-position on the pyridyl ring in order to obtain pioglitazone. With regard to homologation, the court found nothing in the prior art to provide a reasonable expectation that adding a methyl group to compound b would reduce or eliminate its toxicity. Based on the test results of the numerous compounds disclosed in Sodha II, the court concluded that “homologation had no tendency to decrease unwanted side effects” and thus researchers would have been inclined “to focus research efforts elsewhere.” *Id.* at 383. Indeed, several other compounds exhibited similar or better potency than compound b, and one compound in particular, compound 99, that had no identified problems differed signifi-

cantly from compound b in structure. *Id.* at 376 n. 51. Moreover, Dr. Mosberg agreed with Takeda's expert, Dr. Danishefsky, that the biological activities of various substituents were "unpredictable" based on the disclosure of Sodha II. *Id.* at 384-85. The court also found nothing in the '200 and '779 patents to suggest to one of ordinary skill in the art that homologation would bring about a reasonable expectation of success.

As for ring-walking, the court found that there was no reasonable expectation in the art that changing the positions of a substituent on a pyridyl ring would result in beneficial changes. Dr. Mosberg opined that the process of ring-walking was "known" to Takeda, but the court found that testimony inapt as it failed to support a reasonable expectation to one of ordinary skill in the art that performing that chemical change would cause a compound to be more efficacious or less toxic. *Id.* at 382. Moreover, Dr. Mosberg relied on the efficacy data of phenyl compounds in Sodha II, but the court found those data insufficient to show that the same effects would occur in pyridyl compounds.

Alphapharm relies on *In re Wilder*, 563 F.2d 457 (CCPA 1977), for the proposition that differences in a chemical compound's properties, resulting from a small change made to the molecule, are reasonably expected to vary by degree and thus are insufficient to rebut a prima facie case of obviousness. In *Wilder*, our predecessor court affirmed the Board's holding that a claimed compound, which was discovered to be useful as a rubber antidegradant and was also shown to be nontoxic to human skin, would have been obvious in light of its homolog and isomer that were disclosed in the prior art. The evidence showed that the homolog was similarly nontoxic to

the human skin, whereas the isomer was toxic. The court held that "one who claims a compound, per se, which is structurally similar to a prior art compound must rebut the presumed expectation that the structurally similar compounds have similar properties." *Id.* at 460. While recognizing that the difference between the isomer's toxicity and the nontoxicity of the homolog and claimed compound "indicate[d] some degree of unpredictability," the court found that the appellant failed to "point out a single actual difference in properties between the claimed compound and the homologue," and thus failed to rebut the presumption. *Wilder*, 563 F.2d at 460.

We would note that since our *Wilder* decision, we have cautioned "that generalization should be avoided insofar as specific chemical structures are alleged to be prima facie obvious one from the other," *Grabiak*, 769 F.2d at 731. In addition to this caution, the facts of the present case differ significantly from the facts of *Wilder*. Here, the court found that pioglitazone exhibited unexpectedly superior properties over the prior art compound b. *Takeda*, 417 F.Supp.2d at 385. The court considered a report entitled "Preliminary Studies on Toxicological Effects of Ciglitazone-Related Compounds in the Rats" that was presented in February 1984 by Dr. Takeshi Fujita, then-Chief Scientist of Takeda's Biology Research Lab and co-inventor of the '777 patent. That report contained results of preliminary toxicity studies that involved selected compounds, including pioglitazone and compound b. Compound b was shown to be "toxic to the liver, heart and erythrocytes, among other things," whereas pioglitazone was "comparatively potent" and "showed no statistically significant toxicity." *Id.* at 356-57. During the following months, Takeda per-

formed additional toxicity studies on fifty compounds that had been already synthesized and researched by Takeda, including pioglitazone. The compounds were tested for potency and toxicity. The results were presented in another report by Fujita entitled "Pharmacological and Toxicological Studies of Ciglitazone and Its Analogues." Pioglitazone was shown to be the only compound that exhibited no toxicity, although many of the other compounds were found to be more potent. *Id.* at 358.

Thus, the court found that there was no reasonable expectation that pioglitazone would possess the desirable property of nontoxicity, particularly in light of the toxicity of compound b. The court's characterization of pioglitazone's unexpected results is not clearly erroneous. As such, *Wilder* does not aid Alphapharm because, unlike the homolog and claimed compound in *Wilder* that shared similar properties, pioglitazone was shown to differ significantly from compound b, of which it was not a homolog, in terms of toxicity. Consequently, Takeda rebutted any presumed expectation that compound b and pioglitazone would share similar properties.

[7] Alphapharm also points to a statement Takeda made during the prosecution of the '779 patent as evidence that there was a reasonable expectation that making changes to the pyridyl region of compound b would lead to "better toxicity than the prior art." During prosecution of the '779 patent, in response to an enablement rejection, Takeda stated that "there should be no reason in the instant case for the Examiner to doubt that the claimed compounds having the specified substituent would function as a hypolipidemic and hypoglycemic agent as specified in the instant disclosure." That statement, however, indicates only that changes to the left

moiety of a lead compound would create compounds with the same properties as the compounds of the prior art; it does not represent that lower toxicity would result. And even if the statement did so represent, it does not refer to any specific substituent at any specific position of TZD's left moiety as particularly promising. As the court correctly noted, the compounds disclosed in the '779 patent included a variety of substituents, including lower alkyls, halogens, and hydroxyl groups, attached to a pyridyl or thiazolyl group. As discussed *supra*, the district court found that the claims encompassed over one million compounds. Thus, we disagree with Alphapharm that that statement provided a reasonable expectation to one of ordinary skill in the art that performing the specific steps of replacing the methyl group of the 6-methyl compound with an ethyl group, and moving that substituent to the 5-position of the ring, would have provided a broad safety margin, particularly in light of the district court's substantiated findings to the contrary.

We thus conclude that Alphapharm's challenges fail to identify grounds for reversible error. The court properly considered the teachings of the prior art and made credibility determinations regarding the witnesses at trial. We do not see any error in the district court's determination that one of ordinary skill in the art would not have been prompted to modify compound b, using the steps of homologation and ring-walking, to synthesize the claimed compounds. Because the court's conclusions are not clearly erroneous and are supported by the record evidence, we find no basis to disturb them.

The court properly concluded that Alphapharm did not make out a *prima facie* case of obviousness because Alphapharm

failed to adduce evidence that compound b would have been selected as the lead compound and, even if that preliminary showing had been made, it failed to show that there existed a reason, based on what was known at the time of the invention, to perform the chemical modifications necessary to achieve the claimed compounds.

In light of our conclusion that Alphapharm failed to prove that the claimed compounds would have been *prima facie* obvious, we need not consider any objective indicia of nonobviousness.⁵

2. Scope and Content of the Prior Art

[8] Alphapharm also assigns error to the district court's determination regarding the scope and content of the prior art. Alphapharm asserts that the court excluded the prosecution history of the '779 patent from the scope of the prior art after wrongly concluding that it was not accessible to the public. Takeda responds that the court clearly considered the '779 patent prosecution history, which was admitted into evidence on the first day of testimony. Takeda urges that the court's consideration of the prosecution history is apparent based on its extensive analysis of the '779 patent and the file history that appears in the court's opinion.

We agree with Takeda that the district court did not err in its consideration of the scope of the prior art. As discussed above, the court considered the prosecution history, and even expressly considered one of the key statements in the prosecu-

tion history upon which Alphapharm relies in support of its position that compound b would have been chosen as the lead compound. *Takeda*, 417 F.Supp.2d at 378. In considering the prosecution history of the '779 patent, the court noted that Takeda filed a preliminary amendment on March 15, 1983, in which its prosecuting attorney stated that "the compounds in which these heterocyclic rings are substituted have become important, especially [the 6-methyl compound]." *Id.* The court rejected Alphapharm's assertion that that statement supported the conclusion that compound b would have been selected as a lead compound. Rather, the court found that viewing the prior art as a whole, the prior art showed "that Takeda was actively conducting research in many directions, and had not narrowed its focus to compound b." *Id.* at 379. Thus, while the district court may have incorrectly implied that prosecution histories are not accessible to the public, *see id.* at n. 59, *see also Custom Accessories, Inc. v. Jeffrey-Allan Indus.*, 807 F.2d 955 (Fed.Cir.1986) ("[t]he person of ordinary skill is a hypothetical person who is presumed to be aware of all the pertinent prior art"), the court nonetheless considered the prosecution history of the '779 patent in its obviousness analysis and accorded proper weight to the statements contained therein. Thus, any error committed by the court in this regard was harmless error.

We have considered Alphapharm's remaining arguments and find none that warrant reversal of the district court's decision.

5. The concurrence, while agreeing that the question of the "overbreadth" of claims 1 and 5 has been waived, states further that the 6-ethyl compound, which is within the scope of claims 1 and 5, has not been shown to possess unexpected results sufficient to overcome a

prima facie case of obviousness, and hence claims 1 and 5 are likely invalid as obvious. Since waiver is sufficient to answer the point being raised, no further comment need be made concerning its substance.

CONCLUSION

We affirm the district court's determination that claims 1, 2, and 5 of the '777 patent have not been shown to have been obvious and hence invalid.

AFFIRMED

Concurring opinion filed by Circuit Judge DYK.

DYK, Circuit Judge, concurring.

I join the opinion of the court insofar as it upholds the district court judgment based on a determination that a claim to pioglitazone (the 5-ethyl compound) would be non-obvious over the prior art. The problem is that only one of the three claims involved here—claim 2—is limited to pioglitazone. In my view, the breadth of the other two claims, claims 1 and 5 of U.S. Patent No. 4,867,777 ("777 patent")—which are also referenced in the judgment—renders them likely invalid.

All of the compounds claimed in claims 1, 2 and 5 were included in generic claims in the prior art U.S. Patent No. 4,287,200 ("200 patent"). Unfortunately our law concerning when a species is patentable over a genus claimed in the prior art is less than clear. It is, of course, well established that a claim to a genus does not necessarily render invalid a later claim to a species within that genus. See *Eli Lilly & Co. v. Bd. of Regents of Univ. of Wash.*, 334 F.3d 1264, 1270 (Fed.Cir.2003). In my view a species should be patentable over a genus claimed in the prior art only if unexpected results have been established. Our case law recognizes the vital importance of a finding of unexpected results, both in this context and in the closely related context where a prior art patent discloses a numerical range and the patentee seeks to

claim a subset of that range. See *Application of Petering*, 49 C.C.P.A. 993, 301 F.2d 676, 683 (1962) (species found patentable when genus claimed in prior art because unexpected properties of the species were shown); see also *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1371 (Fed.Cir.2007) (relying on lack of unexpected results in determining that species claim was obvious in view of prior art genus claim); *In re Woodruff*, 919 F.2d 1575, 1578 (Fed.Cir. 1990) (when applicant claims a subset of a range disclosed in a prior art patent, the applicant must generally show that "the claimed range achieves unexpected results relative to the prior art range.").

While the 5-ethyl compound (pioglitazone) is within the scope of the '200 patent, there is clear evidence, as the majority correctly finds, of unexpected results regarding that compound, and therefore its validity is not in question on this ground. However, at oral argument the patentee admitted that the prior art '200 patent also generically covers the 6-ethyl compound, which is within the scope of claims 1 and 5 of the '777 patent, and admitted that there is no evidence of unexpected results for the 6-ethyl compound. Under such circumstances, I believe that the 6-ethyl is likely obvious, and consequently claims 1 and 5 are likely invalid for obviousness. However, the argument as to the overbreadth of claims 1 and 5 has been waived, because it was not raised in the opening brief. In any event, as a practical matter, the judgment finding that the appellants' filing of the ANDA for pioglitazone is an infringement and barring the making of pioglitazone is supported by the finding that claim 2 standing alone is not invalid and is infringed.

